CFTRI-MYSORE
3331
Kwashiorkor.

Kwashiorkor,
Protein malnutrition,
Deficiency diseases,
nutritional diseases,

TMS.

KWASHIORKOR

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BY

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PREFACE

This book describes a disease that has only recently been cognized by organized scientific medicine. It employs a name hich may appear to be new, but is actually very old, having been common use among one African tribe for as long as tradition and emory serve.

The book is a result of a collaboration between a clinician, a thologist, and a research worker. The clinician (H. C. T.) has d over twenty years' experience of the disease, which he first met on after his arrival in Kenya in 1929. It was usually found in sociation with tropical infestations of one kind or another, but as e treatment of the infestations improved with the introduction of w and more efficient drugs, it became possible to recognize and investigate an underlying condition of malnutrition. The fashion the day, and some of the features of the disease, led to the belief at vitamin deficiencies might be of importance in the aetiology. tamin therapy was, however, disappointing. Even without the nvenient—and often erroneously invoked—excuse of infection, e mortality was high and was very little reduced until skimmed-lk powder was used in treatment towards the end of the 1939–45 ır.

The second author (J. N. P. D.), the pathologist, who came to ganda during the war, realized that in terms of morbid anatomy treated cases presented a consistent picture. Alterations in cretory glands suggested a cause for the failure to digest food and e difficulty in curing advanced cases with whole cow's milk. Dr. . D. Thompson, who was working with one of us (H. C. T.) at mpala, for the Medical Research Council, was able to confirm e histological evidence by demonstrating the reduction in the ivity of the pancreatic enzymes and improvement after milk otein had been given. The third author (R. F. A. D.), who arrived Uganda in 1951, contributed his experience of paediatrics and ant feeding, much of which had been obtained in Germany during e immediate post-war period. With Miss Ruth Schwartz, another mber of the staff of the Medical Research Council, he collected ochemical data which was intended to help in the definition of the ease and of the pattern of recovery.

The book has three main sections. The preliminary section c
history, case reports and terminology was written by one autho
(H. C. T.). In the next section, which describes kwashiorkor i
children, the chapters on the clinical findings (H. C. T. an
R. F. A. D.), and on prevention (R. F. A. D. and H. C. T.) a
a joint responsibility ; the chapter on pathology is the concern
one author (J. N. P. D.), as are the chapters on biochemistry an
treatment (R. F. A. D.). The summary is the joint work of a
three authors.

The third section of the book, which describes what is believe
to be protein malnutrition in adults, is by two authors (H. C. T
and J. N. P. D.). The condition is less commonly encountered tha
is kwashiorkor in early childhood, and has been less thorough
studied at Kampala and elsewhere. Biochemical data are still scant
and there are no detailed studies of the response to treatment.
cannot be claimed that there is proof that the condition is identic
with kwashiorkor in childhood. The clinical pictures in adul
and children are similar, and so are the pathological changes, but
is possible that further work will disclose clear differences. A
present the differences are not apparent and until they become
it seems reasonable to talk of kwashiorkor in adults.

The book closes with a chapter (mainly by H. C. T. an
J. N. P. D.) devoted to some of the possible implications of t
problem of protein malnutrition in children and adults. There
much to suggest that acute kwashiorkor in childhood is but t
advanced stage of a common variety of protein malnutrition fro
which many children suffer mildly during their early period
growth. Many adults in the tropics live, like the children, on die
which provide very little protein. It may be that the investig
tion of the effects of protein malnutrition will throw light on ma
facts which at present lack explanation, such as the curious frequen
of certain diseases among African adults, and the rarity of othe

The reading of reports of cases has involved a great deal of specu
tion about exact significance and meaning. Some of the speculatio
must be wrong : but it is hoped that those writers who feel they ha
been traduced, or ignored, will accept the apologies of the prese
authors, who will take any opportunity that may arise in the future
correct the erroneous impressions they have given.

The task of unification of three somewhat disparate literary styl and most of the editorial work, was undertaken by the third author (R. F. A. D.). The repetition that will be found in some chapters has been allowed for two reasons: to reduce the preliminary historical sections to reasonable limits, and to allow the chapters to stand more or less complete and self-contained. The authors have their illusions, of which some have doubtless been exposed, and others may have been successfully concealed: they do not, however, harbour the illusion that there are many people who will want to read all the chapters of a book of this kind. A few conventions have been adopted. Unless a statement is made to the contrary, the phrase 'at Kampala' implies "at Mulago Hospital, Kampala", or "in the Medical School of Makerere College", and a phrase such as 'it has been found at Kampala' introduces a finding of one of the three authors, or within his personal experience.

The large number of personal communications which are mentioned in the text give some indication of the extent to which the authors have to thank their friends for help. The full list of those friends would be very long: of Uganda colleagues, it would include Dr. A. Galloway, Dean of the Medical School of Makerere College, who arranged for a grant towards the cost of preparing the manuscript, Professor E. G. Holmes, Dr. P. W. Hutton, Dr. A. B. Raper, Professor A. W. Williams, and Dr. R. F. S. Hennessey, Director of Medical Services, Uganda Protectorate, who kindly allowed a period of special leave for one of us (H. C. T.) for work on the manuscript, and has given his permission for publication. Of the colleagues outside Uganda, the following must be particularly thanked: Professor A. A. Moncrieff, to whose initial encouragement the work is due, Professor J. F. Brock, Professor A. C. Frazer, Sir Harold Himsworth, K.C.B., Professor A. Kekwick, Professor R. A. McCance, Dr. J. H. Sheldon, Dr. H. W. Sinclair, Dr. Cicely Williams and Dr. Lucy Wills.

One of us (J. N. P. D.) would like to acknowledge his indebtedness to the Colonial Development and Welfare Fund for a grant for research in the pathology of undernutrition, and to the Commonwealth Fund, which made possible a visit to the U.S.A. for the same purpose. He wishes also to express his gratitude to members of the staff and the Medical Librarian of Duke University, North Carolina. Another (R. F. A. D.) has to thank Dr. M. G. Candau, the Director-General of the World Health Organization, for his kindness in arranging the journey through the Central American countries, which brought a realization of the extent to which kwashiorkor had been studied there. Dr. R. C. Burgess, Chief of the Nutrition Division of the same Organization, and Dr. W. J. Aykroyd and Dr. M. Autret of the Food and Agricultural Organization of the United Nations, have generously contributed data of various kinds, and have helped in many other ways.

Finally, all three authors wish to thank Mr. T. N. Salthouse, of Makerere College Medical School, who made most of the photographs that appear in the book, Mrs. D. Milburn, the Medical Librarian of the College, whose aid was greatly appreciated on many occasions, Dr. John Higginson, who contributed the account of the pathology of bone, Dr. S. K. Kon, and the other editors of the *British Journal of Nutrition*, who lent the blocks from which two of the figures have been printed, and Miss V. Pearce, who typed (and re-typed) the manuscript.

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PART I

REPORTS OF KWASHIORKOR IN CHILDREN AND A DISCUSSION OF TERMINOLOGY

Reports of kwashiorkor

Early reports of what may have been kwashiorkor lack the clinical, pathological and biochemical details that make identification certain. In the following list, some early reports, although themselves no more than fragmentary, have been included either because their value has become clear in retrospect, or because they stimulated further exploration. The data presented in the main sections of the book are derived from records which, in the opinion of the present authors, strongly suggest kwashiorkor. Selection of records is necessarily arbitrary, and is based on views which are given in a summary (p. 246) at the end of the section on kwashiorkor in children.

The list is intended to be an indication of the scope of the literature, especially that containing clinical descriptions. It does not include all the papers of detailed technical interest that are quoted elsewhere in the book. It shows the countries in which kwashiorkor has been described, it is roughly chronological, and it gives the terms employed by the authors. The majority of the foreign terms have been translated into English ; others are translated in the text where they are discussed.

Some comments on the geographical distribution of the disease will be found on page 52, and a list of vernacular names is given in the Appendix. Reviews of knowledge about kwashiorkor have been made by various authors, including Bablet (1950), Meiklejohn and Passmore (1951), Scapaticci (1951), Brock and Autret (1952), Davies (1952a), Downs (1952), Levent (1952), Luyken (1952), Clément (1952), Bergouniou, Masseyeff, Péquinot and Trémolières (1953), Ferrari (1953), Janssen (1953) and Williams (1953). The very important contributions to problems of infantile malnutrition in Mexico, mostly made under the direction of Dr. Federico Gomez in the Children's Hospital in Mexico City, include studies of " third degree malnutrition ", a condition which would undoubtedly be called kwashiorkor in other countries, as Gomez, Galvan, Cravioto and Frenk (1952) have pointed out. In addition to the many Mexican papers referred to in various chapters, the following should be consulted for a balanced view of the nutrition of Mexican children : Pagola (1947) ; Gomez, Aquilar and Muñoz Turnbull (1947) ; Galvan (1948) ; Vazquez and de la Torre (1948) and Martiñez (1951). A few other papers may perhaps be cited here with advantage. Comment on the skin will be found in Platt (1945), and on the liver in Himsworth (1947). For a full discussion of oedema, arising for various reasons, including a presumed insufficiency of protein in the diet, see Maver (1920), Youmans (1936) and McCance (1951).

List of Papers giving Details of Established or Probable Cases of Kwashiorkor in Children

	Author	*Date*	*Term used*
Africa			
Algeria	Sarrouy, Raffi and Clausse	1952	Kwashiorkor
Belgian Congo	Cochaux	1937	Avitaminosis
	Van Daele	1938	*Buaki*
	Trolli	1938	Dyschromic oedematous syndrome
	Pieraerts	1942, 1946	Depigmentation and oedema
	Doucet	1946	*Mbuaki*
	Drumel	1946	*Mbuaki*
	Jacques	1947	*Mbuaki*
	Verdin	1948	Undernutrition
	Pieraerts	1949a, b ; 1950a, b, c	Kwashiorkor
	Dricot, Beheyt and Charles	1951	Kwashiorkor
Egypt	Iskandar	1935	Post-dysenteric oedema
	Shukry, Mahdi and el Gholmy	1938	Nutritional oedema
	Hanafy	1947, 1948, 1951	Subacute subnutritional syndrome
French Equatorial Africa	Lieurade	1932	Red children
	Lalouel	1948	*Mbuaki*
French West Africa	Jamot	1918, 1920	*Daçaga*
	Bergeret	1948, 1950 ; 1951	Kwashiorkor
	Auffret and Tanguy	1950	Kwashiorkor
	Grall	1950	Kwashiorkor
	Bergouniou	1952	Kwashiorkor
	Bergouniou and Raoult	1952	Kwashiorkor
	Bergouniou and Trémolières	1952	Kwashiorkor
	Houssiaux	1953	Kwashiorkor

REPORTS

	Author	Date	Term used
ambia	Waterlow	1950, 1951a, b	Malnutrition
old Coast	Williams	1931–32, 1933	
	Purcell	1934	Epidemic dropsy
	Dyce Sharp	1934–35	Kwashiorkor
	Williams	1935, 1938a	Kwashiorkor
	Purcell	1939	Akwashiorkor
	Russell	1946	Malnutrition
enya	Philp	1924–25	Oedema and ascaris
	Procter	1926–27	
	Shaw	1933–34	Nutritional oedema
	Carman	1934–35	
	Gillan	1934–35	Oedema of unknown cause
	Sequeira	1936–37	Gillan's oedema
	Vint	1936–37	Infantile oedema
	Trowell	1937	Infantile pellagra
	Anderson	1937–38	Infantile oedema
	Bell	1937–38	Infantile oedema
	Sequeira	1937–38	Infantile pellagra
	Stott	1948	Kwashiorkor
	Clark	1951a	Kwashiorkor
orocco	Pouhin	1939	Nutritional oedema
	Delon	1950a, b, c; 1951, 1952	Oedema of weanlings
igeria	Smith	1942–43	Malnutrition
	Hughes	1945–46, 1946, 1952	Kwashiorkor and ariboflavinosis
	Jelliffe	1952	Kwashiorkor
yasaland	Shircore	1951	Kwashiorkor
hodesia	Gelfand	1946, 1947–48, 1951–52	Kwashiorkor
outh Africa	Ross	1931	Infantile scurvy
	Kark	1943	Infantile pellagra
	Gillman, Gillman, Inglis, Friedlander and Hammar	1944	Infantile pellagra
	Gillman and Gillman	1945, 1947, 1948a, b; 1951	Infantile pellagra
	Gillman and Gillman	1945a, b, c, d; 1946	Infantile pellagra
	Gillman, Gillman, Till, Mandelstam and Gilbert	1945	Infantile pellagra
	Altmann	1948	Malignant malnutrition
	Altmann and Murray	1948	Malignant malnutrition
	Altmann	1950	Kwashiorkor

	Author	Date	Term used
South Africa	Barker	1950	Malignant malnutrition
	Janssen	1950	Malignant malnutrition
	Janssen and le Roux	1950a, b	Malignant malnutrition
	Klenerman	1950	Nutritional oedema
	Walt, Wills and Nightingale	1950	Malignant malnutrition
	Anderson and Altmann	1951	Malignant malnutrition
	Mirvish	1951	Malignant malnutrition
	Wills	1951	Kwashiorkor
	Jackson	1953	Kwashiorkor
Tanganyika	Latham	1934–35	Gillan's oedema
	Harkness	1949–50	Malignant malnutrition
Tunisia	Caruana, Hamza and Ghileb	1953	Oedematous nutritional dystrophy
	Didier	1953a, b	Oedema disease
Uganda	McConnell	1918	Oedema disease
	Stones	1935–36	Oedema in children
	Trowell	1939–40, 1941–42a, b ; 1943	Infantile pellagra
	Brown and Trowell	1944	Kwashiorkor
	Trowell	1944	Malignant malnutrition
	Trowell and Muwazi	1945, 1945–46	Kwashiorkor
	Holmes and Trowell	1948	Malignant malnutriton
	Davies	1948a, b, c ; 1951	Kwashiorkor
	Trowell	1948–49, 1950a, 1951a	Kwashiorkor
	Welbourn	1951, 1952, 1953	Kwashiorkor
	Smith	1952	Kwashiorkor
	Thompson and Trowell	1952	Kwashiorkor
	Trowell and Davies	1952	Kwashiorkor
	Trowell, Davies and Dean	1952	Kwashiorkor
	Trowell and Dean	1952	Kwashiorkor
	Dean	1952a, b ; 1952 *Proc.* a, b ; 1953	Kwashiorkor
	Dean and Schwartz	1953	Kwashiorkor
Asia			
Assam	Hare	1947	Malignant malnutrition
Ceylon	Jayasekera, de Mel and Cullumbine	1951	Fatty liver disease

	Author	*Date*	*Term used*
	Karunaratne	1951	Kwashiorkor
hina	Chen	1942	Nutritional edema in children
iji	Manson-Bahr	1950–51	Malignant malnutrition
	Manson-Bahr	1952	Kwashiorkor
ndia	Chaudhuri (K. G.)	1948	Malnutrition
	Ramalingaswami, Menon and Venkatachalam	1948	Infantile pellagra
	Ramalingaswami	1949	Malignant malnutrition
	Ramalingaswami and Patwardhan	1949	Infantile pellagra
	Patwardhan	1949–50, 1950–51, 1952	Nutritional oedema syndrome
	Chaudhuri (S.)	1950	Malnutrition
	Achar	1950	Nutritional dystrophy
	Achar, Thangavelu and Benjamin	1950	Nutritional dystrophy
	Gopalan	1951	Kwarshiorkor
	Gopalan and Patwardhan	1951	Nutritional oedema syndrome
	Chaudhuri (K. G.)	1952	Malignant malnutrition
	Malhotra	1952	Kwashiorkor
	Ramalingaswami, Sriramachari and Tulpule	1952	Kwashiorkor
	Srinivasan and Patwardhan	1952	Kwashiorkor
	Venkatachalam, Srikanta and Gopalan	1952	Kwashiorkor
	Achar and Benjamin	1953	Nutritional dystrophy
	Sriramachari and Ramalingaswami	1953	Kwashiorkor
ndo-China	Kérandel	1926	*Bouffissure d'Annam*
	Normet	1926, 1928, 1937a, b	*Bouffissure d'Annam*
	Bablet and Normet	1937	*Bouffissure d'Annam*
	Bablet and Canet	1952	Kwashiorkor
ndonesia	Oomen	1950a, b; 1951, 1953	Malignant malnutrition
	Blankert	1951	
apan	Nagayo	1923	Chichiko dyspepsia
	Arakawa, Wada and Takahashi	1951	Nutritional dystrophy
alaya	Williams	1938b, c	Malnutrition
	Pallister	1940	Infantile pellagra

	Author	*Date*	*Term used*
Malaya	Williams	1940–41, 1947, 1949	Kwashiorkor
	Thomson	1950–51a, b	Malignant malnutrition
Philippines	Stransky	1950	Nutritional dystrophy
	Stransky and Dauis-Lawas	1950a, b	Kwashiorkor
	Stransky, Dauis-Lawas and Lawas	1951	Kwashiorkor
Europe			
France	Ribadeau-Dumas, Mathieu and Lévy	1927	Nutritional oedema
	Caussade and Haushalter	1932	Oedema in infancy
	Mouriquand, Weill and Josserand	1934	Starch oedema
Germany	Czerny and Keller	1906, 1928	*Mehlnährschaden*
	Finkelstein	1924, 1938	*Mehlnährschaden*
Greece	Choremis	1948	Pellagra and nutritional oedema
	Petrides	1948	Hunger oedema
	Choremis	1950	Nutritional dystrophy
Hungary	Véghelyi	1948a, b, 1950a, b	Nutritional oedema
	Véghelyi, Kemény, Pozsonyi and Sos	1950	Nutritional oedema
Italy	Frontali	1927	Starch dystrophy
	Frontali	1947, 1948, 1953	Starchy food dystrophy
	Scapaticci and Florio	1948	Starchy food dystrophy
	Bacchetta	1951	Starchy food dystrophy
Spain	Ballabriga	1950	Nutritional dystrophy
	Torres Marty	1951	Kwashiorkor
North and Central America			
Central America	Autret and Behar	1954	Multiple-deficiency syndrome (Kwashiorkor)
Costa Rica	Peña Chavarría and Rotter	1938	Avitaminotic oedema
	Peña Chavarría, Saénz-Herrera and Cordero-Carvajal	1948	Multiple-deficiency syndrome
Cuba	Vázques	1929	Nutritional oedema
	Castellanos	1935, 1937	Pellagroid-beri-beri
	Vilá and Artola	1936	Pellagroid-beri-beri
	Conesa and Cazanas	1938	Nutritional oedema

	Author	*Date*	*Term used*
Curaçao	Hartz	1949	Pancreatic atrophy and fatty liver
	Van Der Sar	1951	Kwashiorkor
El Salvador	Bolanos	1935	Oedematous cachexia
	Coelho	1935	Oedematous cachexia
Guatemala	Cofiño Ubico and Klée	1938 [1]	Multiple alimentary deficiency
	Flores	1947	Multiple-deficiency syndrome
Haiti	Payne and Payne	1927	Oedema disease
Honduras	Vidal	1938 [2]	
Mexico	Correa	1908	*Culebrilla*
	Carrilo Gil	1935	*Culebrilla*
	Espinosa	1935	Nutritional oedema
	Carrilo Gil	1942	Pellagra
	Gomez	1946	Third-grade malnutrition
	Pagola	1947, 1948	Avitaminosis
	Vértiz	1948a, b	Undernutrition
	Turnbull	1951	Infantile Pellagra
	Gomez, Galvan and Muñoz	1952	Third-grade malnutrition
Panama	Howard and Meriwether	1952	Fat disease of the liver
Puerto Rico	Ortiz	1940	Nutritional oedema
United States	Lewis	1926	Pellagra and oedema
	Dodd and Minot	1936	Edema in infancy
West Indies	Waterlow	1947, 1948a, b; 1951a	Fatty liver disease
South America [3]			
Brazil	Pernetta and de Martino	1942, 1945	Dystrophy
	Carvalho, Pinto, Schmidt, Potsch and Costa	1945	Oedematous multiple-deficiency dystrophy
	Carvalho	1946, 1947	Oedematous multiple-deficiency dystrophy
	Carvalho, Schmidt and Pinto	1947	Oedematous multiple-deficiency dystrophy
	Carvalho and Potsch	1948	Oedematous multiple-deficiency dystrophy
	Dantas	1949 [4]	Pellagra and hunger oedema
British Guiana	Herlinger	1950	Wet marasmus
Chile	Schwarzenberg and Cousino	1938	Oedema and hypoproteinaemia
	Scroggie	1939, 1941, 1946	Multiple-deficiency syndrome

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[1] Published 1942.

[2] See Scott (1939b).

[3] See footnote, p. 53.

[4] See Scott (1950).

	Author	*Date*	*Term used*
Chile	Niemeyer and Iturra	1947	Dystrophy
	Jimenez, dal Borgo and Ortega	1948	Multiple-deficiency syndrome
	Meneghello	1949	Multiple-deficiency dystrophy
	Meneghello, Espinosa and Coronel	1949	Multiple-deficiency dystrophy
	Meneghello and Niemeyer	1949	Multiple-deficiency dystrophy
	Meneghello and Niemeyer	1950	Multiple-deficiency dystrophy
	Meneghello, Niemeyer and Espinosa	1950	Multiple-deficiency dystrophy
	Niemeyer and Meneghello	1950	Multiple-deficiency dystrophy
Colombia	Umaña	1943	Dystrophic oedema
Peru	Krumdieck and Puglisevich	1947	Dystrophy
Uruguay	Guerra, Gianelli and Peluffo	1942	Starch dystrophy
Venezuela	Oropeza	1946	Multiple deficiency dystrophy
	Teruel	1946	Multiple deficiency syndrome

Terminology

There is no shortage of names which can be given to the disease. It is possible that no one term will find acceptance in all countries, however desirable that might be. Very few diseases have a terminology common to the different languages of the world. What is important is to know how closely cases of " kwashiorkor " in Africa resemble cases of " starchy food dystrophy " in Italy and " nutritional oedema syndrome " in India—a matter that can be decided only by considering accurate and complete case records of the three diseases.

The term " nutritional oedema " is unacceptable. Although nutritional or hunger oedema was at one time regarded as being due to protein deficiency, in recent years the tendency has been to regard it as the result of undernutrition due largely to shortage of calories. Hunger oedema was studied during and after the war of 1939–45, in Europe and America, and the results led away from the earlier conception of protein deficiency as the causative factor. At least three different varieties of oedema may be ascribed to a nutritional cause: hunger oedema, the oedema of beri-beri (thiamine deficiency) and that of kwashiorkor. A term which includes the word oedema is unfortunate, for it directs attention to one sign, which may indeed be absent. Adults and children may die of undernutrition and yet show no hunger oedema; in the same way visible oedema, although very common in cases of severe kwashiorkor, is not invariably present in cases otherwise typical, and is present in none of the milder cases.

For the present, it would appear unwise to employ terms that define aetiology too exactly. There are objections against the use of any term carrying the suggestion that multiple deficiencies, especially of vitamins, are necessarily present. Similarly, any term implying that one organ is the main or the sole site of the disease should be avoided. Thus although the liver is usually fatty in kwashiorkor, a term such as " liver steatosis " would be too limited. The same objection applies to terms which might suggest a disease of the pancreas, small intestine, or exocrine glands. The disease process affects the majority, if not all, of the tissues of the body and to indicate any one tissue is to offer too restricted a conception.

Many authors have used the terms " dystrophy ", or " nutritional dystrophy ". The term " dystrophy " appears inadequate, meaning literally " bad nutrition ", and " nutritional dystrophy " might therefore be translated as " nutritional bad nutrition ", which is not very enlightening. Some have tried to choose a more appropriate adjective and to speak of " infantile dystrophy ", or " alimentary dystrophy ", but the use of the word dystrophy, suitable as it may appear to paediatricians in continental Europe and Latin America, is unlikely to commend itself to those who use English. In English the word dystrophy has become restricted almost exclusively to a group of muscular disorders, characterised by severe wasting, and having no relation to malnutrition. Malnutrition is the term which has been most frequently used by British doctors describing cases of kwashiorkor, but by themselves, either " malnutrition " or " dystrophy " are unsatisfactory terms because they do not define the *type* of malnutrition present. There are many types of malnutrition, one of which is kwashiorkor.

Some have considered that the term " protein deficiency " might prove acceptable, or that one might speak of " protein malnutrition" or "protein dystrophy". Protein is, however, a complex substance; there are many types of protein deficiency, one occurring in nephrosis, another after operations, another after burns, and yet another in starvation It is by no means certain how far shortages of total protein, or of certain amino acids, or of factors such as vitamins concerned with protein metabolism, are the cause of kwashiorkor. As explained elsewhere (p. 59), it would be unwise to assume that the intake of calories can be disregarded in considerations of the aetiology. At the present time it is premature to speak of kwashiorkor as "protein deficiency in infancy" or "infantile protein malnutrition".

It is possible that eventually different varieties of kwashiorkor may be detected (p. 66); meanwhile, it seems desirable to group together cases which appear very similar in their clinical picture, pathology, biochemistry, aetiology, and response to treatment.

A name is obviously desirable, and what is better than adopting one of those in use in Africa? This does not create a new terminology, but merely recognizes an existing state of affairs. Long before Czerny and Keller (1906) introduced the typically German term *Mehlnährschaden*, a number of African tribes had recognized and named the condition. Their names related to an observed chain of events. The baby usually fared well while breast-fed and continued to do so unless the mother became pregnant again. The avoidance of pregnancy was made easier by polygamy, under which it was possible to enforce a long period of abstinence from sexual intercourse: pregnancy occurring less than two years after the birth of a child was regarded as a disgrace, for it was realized that the first child would suffer. In the majority of tribes the baby would be prematurely weaned and would often sicken. The parents considered that the second foetus would kill the first child, possibly by poisoning the milk, so that weaning became a necessity. The sickness of the weanling was called *kwashiorkor* among the Ga tribe of Accra, the capital of the Gold Coast, among whom Dr. Cicely Williams (1935) found the disease.[1] There had been earlier descriptions in Africa, Asia and America, but they were inadequate and suggested no acceptable terminology. It is quite certain that the term kwashiorkor does not refer to the red colour of the hair or skin, an unfortunate misunderstanding which has had widespread currency. The term describes the child as "deposed" (Williams, 1933, 1952; and see also Donnelly, 1951; MacPherson and Findlay, 1951; MacPherson, 1953; Moncrieff, 1953); it implies shrewd insight into the protection afforded by breast milk, and into the problems arising at the time of weaning, as well as a hint of the relationship of the disease to over-population and the competition of too many mouths. Like the majority of the terms given to diseases of malnutrition (for instance, scurvy, beri-beri, pellagra), the word arose among the common people. It describes a clinical picture, and even contains a reference to cause. Therein lies its chief merit.

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[1] *Obwosi*, the word used by the Ganda, the chief tribe of the Kampala district, has a precisely similar meaning. Miss F. W. Grant, who lived for some months in a Ga village, told Dr. M. Autret (1953, personal communication) that in the Ga language *kwashi* meant first and *orkor* second. This might be held to confirm the meaning given above.

PART II

THE HISTORY OF KWASHIORKOR

The history of kwashiorkor resembles in some ways that of hunger oedema. There are innumerable references, in popular and scientific literature, in historical fiction and in social history, to hunger oedema, but two world wars had to be fought, and large groups of people subjected to partial starvation, before it was properly investigated, and even now it is accorded a place in few standard text-books of medicine.

Doubtless a careful reading and interpretation of the stories of the ancient world, of folk-lore, of household chronicles and of the older paediatric literature, would reveal many cases of kwashiorkor, but it remained to modern times, and to an assortment of physicians scattered over the tropical parts of America, Africa and Asia, to accomplish its scientific recognition. The physicians worked almost always in isolation from each other. They described their observations under a large variety of vernacular names, often in obscure journals, and although from the very beginning some of the accounts were models of clinical description, the lack of a distinctive pathology and of correlations with biochemical changes prevented the emergence of a clear and complete picture. The pathology and biochemistry of kwashiorkor were not systematically investigated until recent years. The results provided the beginnings of objective description ; until then the disease remained a confused syndrome.

When a doctor has seen case after case in some tropical hospital and finds that the people of the district recognize kwashiorkor as one of their sicknesses, he naturally wonders how and why anything so distinctive could have been missed by the organized efforts of modern medicine. It is ironical that African peasants should have succeeded where the medical profession for so long failed. It is even more pertinent that the ailing of the infant was regarded, until very recently, as an expected and ordinary occurrence. The child usually throve while on the breast, unless that supplier of friendly milk failed; but after weaning there came a time of trouble, which all too often ended in death.

Some early descriptions

Many records of kwashiorkor, or of something resembling it, must be buried in the literature of tropical diseases. The earliest that has been traced was written by Correa (1908) in Yucatan in Mexico, who described a curious disease which was arousing considerable speculation among doctors of his time. It was called *culebrilla*, a term that seems to be used for ringworm, and also for snakeskin. It was found in young children, and its chief sign was an intractable diarrhoea ; there was also pallor of the skin, various skin lesions, and oedema of the legs and feet, and it was usually fatal. The differential diagnosis was considered, especially in relation to scurvy, and it was decided that *culebrilla* was in some way related to nutrition or at least to what was then called ' chronic gastro-intestinal catarrh ' ; it resembled the athrepsia of Parrot, except for the skin changes. A point of difference from scurvy, and one which is even now difficult to understand, was that the disease could be found in the children of families in a good social position, who did not, it was presumed, have a very poor diet. A few years later Guillon (1913) in French Indo-China began to study *Bouffissure d'Annam* (Annam swelling). His work influenced Normet (1926), who later in the same country did so much to describe the clinical picture and pathology of kwashiorkor. At first, however, many workers in Indo-China were to conclude that the disease was entirely due to tropical parasites, a cause that has been invoked whenever kwashiorkor has been described in a new country.

From the end of the first world war until Cicely Williams (1931–32) gave her classical description of kwashiorkor many odd accounts turned up in various places. They were a collection of brief clinical notes, describing new diseases which could not be attributed to the presence of tropical parasites. Thus McConnell (1918) recorded very briefly a new " oedema disease " in Bondo in the West Nile district of Arua, in Uganda. The illness was related to a famine but did not appear whilst the famine was at its worst ; it appeared afterwards. It was characterized by oedema, a reddish-brown discoloration of the skin, sometimes by loose stools, and by a variable degree of anaemia, and the presence of hookworms, although usual, did not explain the whole clinical state. Both adults and children were attacked, and ten out of forty died ; there were, however, no post-mortem examinations. Jamot (1918, 1920) also recorded that a disease, called *daçaga* by the Bandas Lindas o Oubangui-Chari of French Equatorial Africa, had been recognize for at least twelve years, and that a Dr. Lacascade had defined th condition in the previous year as a disease affecting both adults an children. It followed the period of fighting in Africa during th first world war and caused oedema and depigmentation of hair and skin. Jamot was able to confirm the clinical picture from his own experience, and to give detailed notes of five cases. Whole families were affected. An account was given of a mother who had lost two children from the disease, and was found herself to be suffering from it. She also had a young child who had a dermatosis in the perineal region, oedema, discoloured hair and skin, and diarrhoea ; it was therefore considered that she had contracted the disease from the child ! The disease was usually fatal and at post-mortem examination the liver was found to be fatty (p. 128). Hookworms might also be present.

Later descriptions

From the twenties onward the literature of kwashiorkor has been growing. For the present purpose it has been thought advisable to describe separately the contributions made in Africa, in Asia and in tropical America, up to the time—about 1940—when it became obvious that the disease affected poorly-fed infants all over the world. After 1940 parochialism and isolation began to break down, and the progress from that time, if somewhat disorderly, was much more integrated.

Early work on kwashiorkor in Africa, 1920–40

1. *East and West Africa.* In tropical Africa there were few doctors until the present century. When they arrived they were surprised at the frequency with which they found tropical parasites and intestinal helminths, and they were inclined to explain any clinical condition in terms of infestations. " I would like to hang a placard with the words *Ascaris lumbricoides* in big red letters in the outpatient department of every native hospital, and in every dispensary throughout Kenya Colony " wrote Philp (1924–25) at Tumutumu Mission Hospital on the slopes of Mount Kenya, and about 70 miles from Nairobi. He proceeded to describe the various clinical conditions " due to ascaris ", not only abdominal conditions, but also in " a child of 3 years of age . . . oedema of the face,

hands and feet . . . like a case of Bright's disease. Santonin was tried in this case without result . . . (and he) gradually got worse and died." At post-mortem there was broncho-pneumonia; there were also twenty-three ascaris worms, despite the santonin. There were no hookworms. Unfortunately there is no mention that the urine was examined in life or the kidneys sectioned at post-mortem despite the suspicion of Bright's disease, and this cannot be claimed as the first case of kwashiorkor recorded in recent times; it must remain a case of unexplained oedema. It is significant, however, that it was at Tumutumu that Gillan (1934–35) later found the children who provided the material for his excellent description of kwashiorkor, and the experience of one of the present writers (H. C. T.) who visited the hospital on many occasions, supports the belief that Philp was in fact describing kwashiorkor in 1924.

Some two years later, only some fifty miles away, at Fort Hall, Procter (1926–27) discovered cases of oedema in young children, in whom the obvious diagnosis of hookworm disease proved inadequate, for treatment produced no improvement. He usually saw these cases while on safari in the reserve, where the practice of medicine was full of difficulties, and seldom at his new hospital, with its "stone ward and ten beds". The journey to the dispensaries where the children were to be seen might be thirty miles and "often entailed five hours or more of motor travelling", but even so Procter was equal to the clinical novelties encountered. "The disease occurs only in quite young children; the child is nearly always of an extraordinary light colour and is usually brought up on account of swelling of the feet. The only history obtainable appears to be that in a number of cases there had been slimy motions for some time. As the disease progresses, the child becomes pale in colour and the pigment seems to be concentrated into a curious black desquamation which is often noticeable on the arms and legs; cracks and sores are often seen at the bends of the elbows and knees, and there may be a general oedema. The child, as far as my information goes, nearly always dies." This is the first unquestionable description of kwashiorkor; it is as clear as it is brief.

Neither of the investigators in Kenya suggested that the disease was nutritional in origin. Cicely Williams (1931–32), who knew nothing of their work, had come to the Gold Coast Colony in 1928, and at Accra met cases of kwashiorkor at the Princess Marie Louise

Hospital which two of us (H. C. T. and J. N. P. D.) have since visited and found still to have cases of the disease. Her Report to the Medical Department for 1931–32 was boldly headed " Deficiency Diseases in Infants " and she proceeded to describe " a well marked syndrome, not uncommon among the children here which I cannot find described in any of the ordinary text-books. There have certainly been more than ten cases seen . . . The disease is always fatal unless treated very early. It appears to be due to an insufficient diet, such as *kenki* and *kassa* alone,[1] continuing for some months. The disease then makes itself apparent in a fulminating attack, the most marked symptoms being the skin condition. The patient generally dies within a month after this has appeared. . . . The (skin) changes are generally symmetrical and begin as small blackened patches . . . (The skin of the whole body) generally shows some degree of depigmentation . . . The fact that this disease is found in people living too exclusively on a maize diet makes it at any rate comparable to pellagra. The differences are obvious—but there are also points of similarity . . . (The) skin changes are extensive and well marked and entirely characteristic . . . Persistent peevishness . . . Anasarca is slight . . . Stools apt to be loose and undigested, no ova or parasites . . . Urine—trace of albumen sometimes . . . Liver is enlarged . . . Age of incidence is from 1–3 years old . . . At post-mortem nothing definite was found except a pale, fatty, and almost diffluent liver." Details of two post-mortems were given and also a record of one case where a cure was affected by continuing breast-feeding and adding condensed milk. There was no attempt to name the disease in this first communication, and the term kwashiorkor does not occur, but the main clinical features had been described, post-mortems had been performed, the first cure had been achieved by milk, and the disease had been ascribed to malnutrition.

Meanwhile Lieurade (1932) in the same year, while knowing nothing of any previous work, was moving up the waters of the Sanaga river of the French Cameroons vaccinating the inhabitants of the N'Gaoundere district. On his way he noticed " les enfants rouges ". It was medicine as practised on safari, and the clinical description was brief. Young children aged 2 to 5 years were noticed because of their skin colour (" *leur peaü peut atteindre la teinte de l'acajou clair* ") and their hair, which might even be blond.

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[1] *Kenki* and *kassa* were foods prepared entirely from maize.

They also showed flaking of the skin and oedema; they had diarrhoea and they were apathetic. The author regretted his inability to study the condition more thoroughly and we share his regret, for undoubtedly this was kwashiorkor.

The next year (1933) Cicely Williams issued a comprehensive clinical description and amplified her previous note, still without using the term kwashiorkor. She stressed the importance of the dermatosis as a diagnostic sign, but emphasized the distinction from pellagra. Her views were subjected to detailed criticism by Stannus (1934), who maintained that the condition was pellagra, a disease of which he had had considerable experience in Nyasaland, and on which he therefore spoke with authority.

Meanwhile in Kenya some knowledge of the disease was accumulating, but in complete ignorance that the condition had been described in the Gold Coast. The present writer had been interested in the condition since his arrival in the Colony in 1929, and on the 13th December, 1933, a case was shown at a clinical meeting in Nairobi of the British Medical Association (Kenya Branch) by Dr. A. R. Shaw (1933–34). "He had seen some half a dozen cases, in infants of one, two or three years . . . and he drew the attention of the meeting to this disease, as a new clinical entity." Dr. R. A. W. Procter, Dr. C. R. Phillip and the writer all said they had seen similar cases, and that frequently the preceding history was one of the passage of blood in the stools. The general feeling of the meeting was that it was "a nutritional oedema of unknown cause". At that time in some of the standard text-books of medicine "nutritional oedema" was considered to be due to protein deficiency, and much progress might have been achieved if action had been taken on the collective views of the Nairobi doctors. Unfortunately the suggestion that the condition was pellagrous was soon to divert attention from protein to the vitamin B complex.

At Tumutumu Hospital Gillan had taken over from Philp; it is not known if there was any discussion about the oedema which occurred in children, and its relationship to ascariasis, but soon Gillan (1934–35) wrote the first full clinical description of kwashiorkor in East Africa. He was in complete ignorance of the work in West Africa and of the views of Stannus (1934); his clinical description was very clear and contained a few new points. He minimized the importance of the dermatosis, which he called a mere "patchy desquamation of the skin", and made no reference to the possibility of pellagra. Apart from this the clinical description was comprehensive and three cases were noted in adult females. The stools were often loose, and a " pale, greasy or soapy looking stool . . . (was regarded) . . . as typical of such cases " ; microscopically " starch granules . . . (and) much vegetable debris . . . were present ". He therefore discussed in some detail a possible relationship to coeliac disease. Two post-mortems were performed, and fatty livers were found. Gillan did not appear to entertain any idea that the disease might be due to malnutrition ; rather did the diarrhoea and the fatty liver suggest to him a specific infective agent in the small intestine.

Stimulated by the account given by Gillan, Latham (1934–35) reported the first case of kwashiorkor in Tanganyika. As he knew only of Gillan's work, he did not consider the possibility that the disease was nutritional.

The work of Cicely Williams (1931–32 ; 1933) had not passed quite unheeded in the Gold Coast. Dyce Sharp (1934–35) described another typical case in the *Transactions* of the Royal Society of Tropical Medicine and Hygiene. This journal circulated extensively in the Tropics, and through it various workers at once become conscious that the disease was not purely local. Almost immediately Carman (1934–35) in Kenya drew attention to the fact that much work on the disease had been proceeding in and around Nairobi, and for the first time East Africa and West Africa became conscious of a common problem. Stones (1935–36) at the Mengo Hospital, Kampala, set to work to cull the excellent notes of that hospital, and abstracted four typical cases, adding details of a fifth case which he had himself treated. These cases were the first to be recorded in Uganda, where there had been much confusion with congenital syphilis, and it was appropriate that Stones should allude to the fact that the " mother stated that she had herself suffered from syphilis ". Stones was a careful clinical observer, but he dismissed the light colour of the negro hair. He said it " is common in sick Africans, and is not of significance ". The dismissal reflected the opinion of all workers, including the writer, at that time.

Stones was apparently not aware of a letter by Loewenthal (1935–36) which had been written slightly earlier than his own communication and published in the same journal. The letter was another link between East and West Africa. It drew attention, however, not so much to the work of Cicely Williams (1933) as to the opinion of Stannus (1934) that kwashiorkor was nothing but pellagra. Loewenthal did not claim any definite experience of pellagra, or even to have seen any cases of kwashiorkor, but he was particularly interested in dermatology, and had made contributions to the study of disease of the skin among Africans in East Africa. He accepted the verdict of Stannus (1934), who was "probably our leading authority on the subject of pellagra and other food deficiency diseases in African natives, and in the light of his reasoned argument (suggested) that these cases be regarded as pellagra until evidence to the contrary is more convincing". When to the opinion of Stannus in London could be added that of Loewenthal in Uganda, and later that of Sequeira (1937–38) in Kenya, who also insisted that the dermatosis was certainly pellagrous, there appeared to be little reason to demur.

At least in Kenya, however, there was a feeling of uncertainty which was indicated by the terminology used by Vint (1936–37), who in the course of recording 1000 post-mortems in Nairobi gave notes of eight cases of "infantile oedema". He stated that he had seen no cases in adults, and in this differed from Gillan (1934–35; see above, p. 17). Vint noted that the liver was fatty and drew attention to the atrophy or absence of the thymus gland. His eight records were all of cases studied by one of us in Nairobi and soon described elsewhere (Trowell, 1937). Anderson (1937–38) referred briefly to kwashiorkor in Kikuyu country when he was discussing the diet of that tribe. He noted that early cases would improve if given enough milk. Elsewhere in the same article he noted that milk "is seldom given to children", but he did not stress the relation between these two observations. He seemed to feel that the condition might "be due to vitamin deficiency". The idea of pellagra was beginning to germinate in East Africa. It is interesting to note that in some of the records of his cases which Anderson most kindly put at our disposal in 1952 the value in treatment of milk rather than vitamins is emphasized. It is a pity that Anderson's work was never published in full: its potential value is now clear, and makes one wonder how much more excellent observation has remained in obscurity.

The publications in East Africa took little note of a further development in the discussion on the relationship of kwashiorkor to pellagra. Cicely Williams (1935) made a further statement, in the *Lancet*. Two years had elapsed since her previous communication (1933), which had been adversely criticized by Stannus (1934), and meanwhile she had seen some " sixty cases in three years among patients at the Children's Hospital, Accra ". The oldest child was 5 years old, and it seemed that the disease did not occur among adults. The local name was *kwashiorkor*. The clinical picture was portrayed in detail, but once again the dermatosis was given great prominence, and it was suggested, although not explicitely stated, that all cases eventually developed it. Since the burden of the article was the distinction between kwashiorkor and pellagra, it was unfortunate that the former disease was found always " associated with a maize diet ". But on three points Cicely Williams remained adamant : firstly, that she was describing a new clinical entity ; secondly, that it was due to malnutrition ; thirdly, that it was not pellagra.

In the next issue of the *Lancet*, Stannus (1935) replied. He lodged objections to " the use of a West African native word as the title of an article ". He dismissed as superstition the idea that the disease occurred only in an infant who was " deposed " by the conception of another foetus. He insisted that the description and the photographs of the dermatosis were of pellagra. Having adopted this point of view he emphasized every other point which supported the diagnosis of pellagra.

One of us (H. C. T.) began a systematic study of the disease in 1933, when it was considered to be a " nutritional oedema of unknown cause ". Many sections were made, especially of the skin, liver, and other organs, and a series of photographs of the skin was taken by Dr. W. M. Brown of Tumutumu Hospital, who was deeply interested in the disease. The clinical and post-mortem records, and the first draft of a paper, were taken to London, where they were studied by Dr. Stannus. Dr. Stannus also examined the photographs and very kindly allowed the addition to the manuscript of a note saying that " after seeing the photographs . . . (he was) . . . further confirmed in his opinion . . . that the skin condition was certainly typical of pellagra in native children ".

Following the meeting with Dr. Stannus, and discussion of the cases with him towards the end of 1935, it was decided to regard the disease as pellagra with certain anomalous features—oedema, anaemia, and a fatty liver—which were ascribed to a deficiency of the vitamin B complex and of animal protein. There was some discussion of the relationship to nutritional oedema, but no estimation of the serum proteins. Treatment was by milk and Marmite, and only six children out of twenty-six were lost. In addition to a comprehensive description of the disease, an attempt was made to review previous publications from other parts of Africa, so that all work in East and West Africa became a unity. The article, making a synthesis of nutritional oedema and pellagra, and calling the disease "infantile pellagra", was published in 1937 (Trowell, 1937).

In the sheltered backwaters of East Africa, to which mails then travelled slowly, the first news of the publication came in a cable from the United States. Its length was as great as its contents were mysterious. It contained an offer to send large amounts of a substance, called nicotinic acid, concerning which no one in Uganda had any information. The nicotinic acid arrived and was tried. Almost all the children died. It was not to be the first mistake or the last disappointment.

In 1938, Cicely Williams, who was then in Malaya, published two other articles which were of great interest. The first (1938a) surveyed the problems of child health in the Gold Coast, and showed excellent photographs of unsatisfactory growth, for which malnutrition was held chiefly responsible, the diet having an excess of bulky carbohydrates, and lacking proteins and fats. Although she referred to her description (1935) of kwashiorkor, the author did not invoke that disease as the cause of the growth failure she was illustrating. The difficulty in defining what constituted the disease is obvious in the second article (Williams, 1938b), which was entitled "Clinical ascariasis in children". The effects of the worms in children in Malaya, the Gold Coast and elsewhere were said to include peevishness, anaemia, oedema, a slight albuminuria, and dyspigmentation of the skin ; the hair might be sparse, dry, staring and reddish in colour instead of black ; there might be attacks of diarrhoea and in a chronic case "the food is passed per rectum practically unaltered in appearance and only slightly more offensive in smell". Here was the complete picture of kwashiorkor with the exception of the dermatosis, and yet the disease was not mentioned, although it was recognized that in some cases there was no discoverable evidence of the presence of the worms. It is now known that in Malaya, the typical dermatosis is rarely seen in cases of kwashiorkor (Williams, 1940–41) : in 1938, its presence was obviously an indispensable part of the diagnosis.

About the same time, a further attempt to summarize the literature was made by the present writer (Trowell, 1939–40). He was not then aware of either of the articles published by Cicely Williams in 1938, and made no reference to them. Notably clear accounts of kwashiorkor had been found in the paediatric literature of tropical and Central America; a few possible cases from Europe were mentioned, and reference was made to the work of Normet (1926) in Indo-China. Kwashiorkor was no longer a disease restricted to tropical Africa, but was present in many other places, including Mediterranean countries and the United States of America. In this article increased stress was laid on the presence of the oedema; there was considerable discussion of its significance and pathogenesis, and in the summary it was given first in the list of symptoms. The suggestion which emanated from the literature of tropical America, that the oedema was due to beri-beri, was rejected, and the proposed term of Castellanos (1935) *pelagroide beri-berico*—was found unacceptable largely because there was no evidence of peripheral neuritis or of heart failure either in life or at autopsy, and no improvement when thiamine was given even by injection. It was, therefore, necessary to consider the possibility of "nutritional oedema", which was at that time thought to be due to protein deficiency, and to be accompanied by marked changes in the serum proteins (Schittenhelm and Schlecht, 1919; Von Jaksch, 1918; Jansen, 1918, 1920; Youmans, 1933, 1936; Youmans, Bell, Donley and Frank, 1932, 1933). A few sera from Kampala cases of kwashiorkor had been flown to Nairobi, as at that time the estimation of the various serum proteins was not possible in Uganda. The analysis was performed by Dr. D. Harvey, who had, however, some misgivings about the reliability of the results obtained, owing to the delays in transit. Detailed figures were therefore not given, but it was recorded that "the oedema is associated with a decreased serum albumin which suggests its relationship to nutritional oedema and at the same time its treatment". This appears to be the first reference to any estimation of the serum proteins in kwashiorkor in Africa: the first estimation in Central America (p. 31) must have been almost exactly contemporaneous. The opinion was maintained that kwashiorkor was not a new disease, but merely an unusual grouping of deficiencies of protein and the pellagra-preventive factors. The view was expressed that prevention perhaps involved more than nicotinic acid and it was hoped that some unrecognized vitamin of the B complex might be the substance that was needed.

Cicely Williams (1940–41), who was still in Malaya, replied across the shadows of the second world war. She maintained her previous position. She started on a modest note, discussing the nomenclature, but not clinging too possessively to her own term kwashiorkor. It was difficult to define the disease; it had "no sharp edges". She was unable to include cases which had only oedema and brown hair. "The depigmentation of skin and hair and the straightening of the hair that occurs in African children with 'infantile pellagra' has been frequently noted. But this is in no way specific. The more marked cases of depigmentation occur in Africans with the more chronic conditions such as ascariasis, quite apart from any sign of pellagra whatever. In Singapore, we frequently see children with marked oedema of the face and extremities; the hair is dry and sparse, and though they may produce large numbers of ascarides (Williams, 1938b) I have only seen one case that developed 'infantile pellagra'." In other words, the presence of the dermatosis remained essential to the diagnosis.

In his next paper, the writer (Trowell, 1941–42a) stated some of the uncertainties in diagnosis and some of the difficulties in treatment. "I have been disappointed by the treatment of the disease by nicotinic acid alone." The disease was almost certainly due to multiple deficiencies, "the major ones being those of nicotinic acid, riboflavin and protein, the latter producing a marked nutritional oedema. Possibly as yet the main deficiency is not known." Within a few weeks of the publication of the article all further correspondence with Malaya was interrupted by the Japanese. Dr. Williams was interned as a prisoner-of-war for four years, and was herself to experience the rigours of malnutrition. When eventually she and the writer met for the first time at the end of 1945, other research work had resolved many points of disagreement. By then kwashiorkor was a clinical entity and well separated from pellagra. The dermatosis was not considered to be an essential feature, but only to affect cases shortly before death. There were many minor cases of the disease. Kwashiorkor was due to protein malnutrition.

Meanwhile, Purcell (1939) had issued from the Gold Coast the first monograph to be written on kwashiorkor; unfortunately much of the literature was not available to him and he mentioned none of the work in East Africa, apart from the early communication of Gillan (1934–35). He built up clinical observations from first principles; he did not start with any preconceived idea that he should study only cases with the dermatosis of Akwashiorkor (he adopted this term, although he seems to have considered " infantile pellagra " more apt), or only cases with oedema. He regarded kwashiorkor as standing at the apex of a huge pyramid of malnutrition. This point of view did not commend itself to some of those who reviewed the monograph—for instance Scott (1939a), who felt that tropical infections, such as ancylostomiasis, might be ameliorated " when a nourishing diet is taken, but these (infections) are not, therefore, ascribed to malnutrition ".

In the later sections of Purcell's book the whole conception of a broad pattern of malnutrition was built up ; minor cases were described, and many new observations of associated conditions were made. Amongst these were enlargement of the parotid and lachrymal glands, cancrum oris, necrosis of the skull bones under a pressure sore, a nephrotic type of nephritis, the precipitation of the dermatosis of kwashiorkor by an attack of measles, an eczemoid eruption in the external auditory meatus, the potbelly of chronic intestinal dyspepsia, and the hypotonic muscles which produced knock-knee. Finally there is a comment on the adult. " The men of Akim are generally regarded as being weak-willed, lazy and cowardly. They are not eligible for the army as they lack stamina. Such inferiority may be attributed to their diet."

2. *Belgian Congo.* The earliest workers in the Belgian Congo did not realize for several years that malnutrition of the kind they saw was being investigated elsewhere, and their initial uncertainties were similar to those which attended the investigation of kwashiorkor in the British territories, and of *Bouffissure d'Annam* in Indo-China. Thus Dumont (1934) was faced with the diagnostic problem which had confronted Normet (1926) in Indo-China and McConnell (1918) in Uganda : he found weak, thin adults, suffering from anorexia and diarrhoea. No tropical infection appeared to be responsible, and he therefore considered that the condition was due to malnutrition. He used the term " avitaminosis ", and behind this vague title the syndrome in adults remained concealed and unexplored for many years. Cochaux (1937) was apparently in ignorance of any other work when he was investigating the disease called " *Nzadi* " or " *Lupussu* " among the inhabitants of Kasai in the Belgian Congo He was quite clear that it occurred among both adults and infants and was often associated with helminthiasis.

In 1938 Trolli published a symposium on a new syndrome investigated in the Kwango district. Trolli was the first Director of the medical organization known as *Fonds Reine Élisabeth pour L'Assistance Medicale aux indigenes du Congo Belge* (Foréami), and this distinguished association of physicians has remained actively interested in kwashiorkor ever since his time (see Mouchet, 1950–51). The symposium included contributions from Mercken, Pavese, Haddad, Lamote, Georgiades, Van Daele, Orlovitch, Renvillard and Tessitore. Although Trolli was aware that kwashiorkor had been investigated in East Africa and on the West Coast, it is probable that this influenced but little his own appraisal of the problem, and that most of his assistants approached it as if it was completely new. His definition of the disease differed in one apparently important respect from that which had become current in the British Colonies. There, much emphasis had been placed on the presence of the dermatosis, but in Kwango the dermatosis was not to be found. He described a combination of oedema, a waxy appearance of the skin, discoloured hair, severe anaemia, apathy and feebleness. One or two of the assistants reported cases in adults ; thus Van Daele saw fifteen cases in men and fifty-seven cases in women, and one hundred and forty-nine cases in children. The majority of observers reported that the disease was almost restricted to young children, especially those who had been recently weaned. All were agreed that among these children the condition was rapidly fatal.

In addition to contributing to the symposium, Van Daele (1938) also gave his findings in a separate article discussing " *Buaki*—Maladie de la peau rouge " among the inhabitants of the Kwango district. He had seen many cases at all ages but his seven recorded patients were children at or near adolescence, suffering from oedema, redness of the skin and hair, and moderate anaemia. Some had very scanty ova in the stools but others had none at all, so that helminthiasis seemed unlikely to be a consistently important factor in the aetiology. The disease was particularly likely to appear in neglected women and in orphans. It was suggested that a general failure of nutrition was present, producing something akin to hunger oedema, and it was said, indeed, that the condition usually responded favourably to a mixed diet.

These contributions from the Belgian Congo raised again the question of whether or not the dermatosis was an essential feature of the disease. Although the dermatosis was thought by workers elsewhere to constitute a sure " hall-mark " and to demonstrate a relationship to pellagra, the Congo workers made their diagnosis on the other signs, all of which were not to be explained by a helminthic infection. No further advance seems to have been made before 1942, when Pieraerts made his first contribution to the study of the disease. He had already been working for several years in the Kasai, and had observed that although sporadic cases were always appearing—usually in an abandoned child, or in one who had been suffering from a chronic gastro-intestinal illness—the main incidence was seasonal, the season being that time of year when the diet was almost exclusively cassava. Depigmentation, oedema and anaemia were important features.

Early work on kwashiorkor in Asia, 1913–40

Early work on kwashiorkor in Asia preceded most of the work in Africa and in tropical America. It emanated entirely from the one area of Indo-China, and almost entirely from one man—Normet. In certain respects it followed the same course as the work in Africa, for there was the same difficulty in determining whether the disease differed in adults and in children (among whom it was seldom described), and the same uncertainty about tropical parasites and other infections as the possible cause of all features of the disease. The work was notable for the accuracy of its clinical insight, and included the first attempt to describe the pathology of the disease.

Normet (1926), always ascribed the name *La bouffissure d'Annam* to a M. Guillon who had drawn attention to the disease as early as 1913 and had noticed that adults and children easily developed generalized oedema and effusions in the serous sacs, especially the peritoneal cavity. Although most doctors had ascribed the disease to malaria, hookworms, ascaris or syphilis, an outbreak which assumed almost the character of an epidemic led Normet to more thorough investigation. He was soon forced to abandon any idea that parasites might provide the sole explanation, and to consider the possibility of malnutrition. " Annam Swelling " occurred only among coolies and poor agricultural labourers, and was never seen among the upper classes, nor among those who lived by the sea and ate fish. Although present at all seasons of the year, it became common during the dry season, or if the storms had destroyed much of the crops. The disease caused general wasting, which was masked, however, by the oedema ; when the oedema disappeared under treatment, the extreme atrophy of the muscles became obvious. The blood-pressure was low, and the skin was dry. Anaemia was very variable, the haemoglobin being as low as 10 per cent of normal in some cases and up to 50 per cent in others. There were no signs of paralysis, so that beri-beri was excluded.

The blood urea was always below 25 mg. 100 ml., and the total daily excretion of nitrogen was always very small. The patients sometimes died suddenly and unexpectedly, and at post-mortem the anaemia was almost the only abnormality. Helminths were often but not invariably present, but as they were nearly always found in coolies at post-mortem, whatever the cause of death, it was not considered that intestinal parasites could be more than a precipitating factor. Everything pointed to a disturbance in nitrogen metabolism and therefore Normet tried intravenous injections of the amino acid glycine. He considered this was almost a specific form of treatment, for the oedema rapidly disappeared, disclosing a mere skeleton covered with skin, and an enormous appetite developed which produced a rapid gain of weight. The anaemia responded slowly but was helped by iron. Normet considered that the disease was a new clinical entity, that it was a major cause of death in Indo-China, and that the mortality in untreated cases was 95 per cent.

In the same year Kérandel (1926) joined issue with Normet. Upon one thing there was complete agreement: *Bouffissure d'Annam* was the chief cause of death in the country. Concerning aetiology there was no agreement, and some of the local doctors invoked malaria, hookworm disease or beri-beri. Thiroux (1920), who according to Kérandel worked on severely anaemic cases of *Bouffissure d'Annam*, ascribed the condition to the presence of multiple infections; thus hookworms might affect 80 to 100 per cent and malaria 50 per cent, and the Wasserman reaction might apparently be positive in as many as 95 per cent.

Normet (1928) replied to Kérandel and did not recant. He rejected completely the view that various infections and particularly ancylostomiasis, could be responsible for the disease. He reiterated that it was characterized by peculiar changes in the blood and urinary urea, and that infections were often no heavier than in coolies who were apparently healthy. In addition, he was now able to give certain facts about the pathology of *Bouffissure d'Annam*, and he described in detail the results of two autopsies, on a child of 12 years and a man of 60. He considered that the histological changes found in the liver and pancreas (pp. 128, 144) explained the severe metabolic disturbances, of which one of the most constant was the failure to digest food. The alimentary defect, which was, in his opinion, the essential feature of the disease, was thought to be due to protein deficiency.

Some ten years later Normet made his final contribution. His studies with Bablet (Bablet and Normet, 1937) had shown that *Bouffissure d'Annam* had a distinctive pathology; none of the lesions could be ascribed to tropical parasites, so that he was confirmed in his opinion that the disease was a true clinical entity even if its precise aetiology was still obscure. It was considered that the condition was largely due to protein deficiency with the vitamin B complex playing an ancillary part. High protein diets by themselves were not curative, for they could not be digested; the failure of digestion was due to the pancreatic lesion, while the hepatic lesion might impose further complications on the metabolism of many foods. The disease attacked mainly adolescents and adults. No attempt was made to describe any condition occurring commonly among weanlings. Finally, Normet considered that a very large number of the adult population had the disease, at least in a mild form, even if they showed no oedema (Normet, 1937a, b).

The first indisputable account of a case of kwashiorkor in Malaya was that of Pallister (1940), who saw a Chinese infant with the disease. He realized at once that it was kwashiorkor because the characteristic dermatosis was present. He made no mention of the work of Normet, but by his reference to the African descriptions, he united Asian and African knowledge.

Early work on kwashiorkor in tropical America, 1908–40

The work in tropical America followed almost completely the same lines as that in tropical Africa and in tropical Asia, and was indeed in many ways more prolific. From 1920 to 1939 more papers were to emerge from tropical America than from any other area, but still the work remained isolated, and unrelated to research carried out in Africa into kwashiorkor, or in Asia into *Bouffissure d'Annam*. Slowly the acute phase of kwashiorkor in infancy became differentiated; always there was keen debate concerning its relationship to tropical infections, and finally the disease became confused with a deficiency of the vitamin B complex.

Reference has already been made to the inquiry of Correa (1908) into the aetiology of *culebrilla* in Mexico; later work, especially that of Carrilo Gil (1935), has suggested that this term usually described the characteristic dermatosis of kwashiorkor. Shortly after McConnell (1918) had described the "oedema disease" at Bondo in Uganda, the Americans Mann, Helm and Brown (1920) described in adults a new clinical entity—"An oedema disease in Haiti". They were fully cognizant of nutritional oedema, or "war oedema" as it was then called, but they concluded that a distinction from that condition should be made, if only because in Haiti the onset was rapid, the response to diet was poor and mortality was high. The absence of cardiac failure and of peripheral neuritis excluded beriberi, and no cause of anaemia explained the condition. Intestinal parasites could not be responsible because none were to be found in more than half of the cases. At post-mortem there was little that was definite, but there was generally a "slight to moderate amount of cirrhosis".

Mann (1924) amplified his observations on adult prisoners, among whom, especially if they had been vagrants, the disease was very common, so that there were more than 1000 deaths in twelve months. The same condition occurred among civilian adults but there was no hint that it occurred among infants, or was accompanied by a dermatosis or by dyspigmented hair. It is possible that the condition had a remote ancestry, because Mann traced a reference to a "Mal d'Estomac" described in a "Manuel des Habitants de Saint Domingue", published about 1777. (The title page of the book was lost and the exact date was uncertain.) Negroes were described as being quickly attacked by a disease characterized by cachexia, dropsy, and gastro-intestinal upsets. It is probable that the diets in the prisons of Haiti were extremely unsatisfactory in the period observed by Mann. Their exact composition, and whether they were of adequate caloric value are not known, but from internal evidence it seems likely that the chief staple was corn meal (maize meal). Mann advocated increasing the amount of green vegetables in the diet and raising the proportion of germ and pericarp in the corn meal. When these suggestions were adopted the disease practically died out of the prison, although Wickersham (1929) ascribed its disappearance not only to Mann's changes, but also to an increase in the amount of animal protein.

Other American doctors (Payne and Payne, 1927) were led to inquire into "an edema disease among children in the republic of Haiti". It occurred most commonly in the second year of life, and the children improved after receiving milk, butter and ripe bananas.

Nevertheless there were many deaths among the recorded cases. The onset was associated with oedema and diarrhoea ; the skin became pale and the hair was usually lost, but there was no mention of a characteristic dermatosis. Slowly it was recognized that in addition to the oedematous children there were many others who were merely wasted, with thin and weak legs and large swollen abdomens, " like match-sticks in a potato ", and that this condition of malnutrition preceded the oedematous stage of the disease.

Castellanos (1935) published an extremely complete account of kwashiorkor in Cuba, but made no reference to other work in Africa or Asia or tropical America. It is, therefore, not surprising that he thought he was observing a mixture of deficiency diseases, which should be called *Sindrome pelagroide beri-berico.* There is no evidence that he was aware of the views of Stannus on the identity of pellagra and kwashiorkor. There was an excellent account of the disease as it affected infants, and the first description of the dermatosis in purely white children, although most of the children were coloured or of negroid extraction. The first sign in a white subject was the occurrence of areas of fiery red skin, like patches of scarlatina ; their colour rapidly changed to a dark red and then brownish red, and finally they became dark brown plaques which soon peeled extensively to reveal areas of completely white skin. Unfortunately there were no studies of the pathology or biochemistry of the disease, and no reports of improvement on giving either thiamine or preparations of the vitamin B complex. Nicotinic acid was unobtainable at that time.

In the same year Coelho (1935) wrote about a new disease which was an important cause of infantile mortality in El Salvador. He called it *cachexie hydrique infantile tropicale.* It attacked infants 2 to 3 years old, and two-thirds of them died. He acknowledged another description of the disease (called *caquexia hídrica*) by Goenz in San Salvador, but was ignorant of the work of Castellanos. At postmortem examinations, described in detail by Bolanos (1935), the constant finding was a severe fatty degeneration of the liver.

Two years later Castellanos (1937) amplified his views on *pelagroide beri-berico* as seen in Cuba, and compared it to *culebrilla*—the " ringworm disease " of Mexico (Carrilo Gil, (1935). Illustrations of the skin showed that the *pelagroide beriberico*, the " ringworm disease " and the dermatosis described by Williams (1931–32, 1933) were essentially the same. Vilá and

Artola (1936) also reported cases in Cuba, one white child having a typical skin eruption. The hair was pale in colour and poor in texture. Conesa and Cazanas (1938) gave an account of another white Cuban child in whom xerophthalmia and impetigo complicated the usual picture, giving rise to the belief that a deficiency of vitamin A was mainly responsible. Peña Chavarría and Rotter (1938), described cases of "avitaminotic oedema" in children in Costa Rica, a territory which adjoins Panama. Good illustrations accompanied their article and showed the characteristic dermatosis; diarrhoea was severe and the fatty liver was a constant feature at autopsy. It was considered that the disease seen in Costa Rica was identical with the *cachexia hídrica* of El Salvador, and was allied to "war oedema" as seen in Central Europe. In 1938 Cofiño Ubico and Klée reported the disease in another territory of Central America, Guatemala, and Vidal reported it in Honduras (see Cofiño Ubico and Klée, 1942, and Scott, 1939b). Cofiño Ubico and Klée considered that the oedema was related to the hypoproteinaemia, and noted the abnormal ratio of albumen to globulin in the serum. Vidal noted that the disease occurred in white children and that the desquamation was preceded by a wide-spread symmetrical erythema.

Some of the workers in Central America and the Caribbean area in reporting their observations made references to the work progressing in tropical Africa. One of the most important points in their work lay in the description of the disease in white children unaffected by tropical parasites.

Accounts of the disease continued to appear from time to time in the next few years, most of the South American countries making some contribution,[1] and many different names being used. In 1948 Waterlow published the results of his investigation of "fatty liver disease" in the West Indies (Waterlow, 1948a, b). The investigation was suggested by Professor B. S. Platt, who had seen cases of kwashiorkor in Africa and recognized that the "sugar babies" of the West Indies were suffering from the same condition.

The later history of kwashiorkor, 1940 to the present day

The three streams of knowledge of kwashiorkor from the tropical countries of Africa, Asia and America met soon after the outbreak of the 1939–45 war (Trowell, 1939–40) and became one. From then onwards, the descriptions of new local diseases affecting, apparently, only coolies in Indo-China, or infants in the Gold Coast, became less frequent. Kwashiorkor became a single problem although it still seemed to have no definite aetiology, pathology, biochemistry or treatment, and although there was no large measure of agreement that it was due to malnutrition.

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[1] See footnote, p. 53.

It would be very difficult to summarize all the many papers written about kwashiorkor since 1940, and no attempt will be made here. From time to time, especially from the Mediterranean countries, but also from Central Europe, there came reports of a disease resembling in many respects kwashiorkor ; the reports are in many cases difficult to evaluate, for they were often made by workers unacquainted with the literature of the disease. In other countries, notably India and the West Indies, reports were written by workers who had probably never seen cases of kwashiorkor elsewhere, even if they were familiar with the literature, so that the absence of certain features such as dyspigmentation of the hair, or a characteristic dermatosis, must be taken with some reservation. Knowledge of the essential pathology of the disease lagged far behind, but when eventually established cleared up much confusion. Biochemistry was even slower in making its contribution although it now bids fair to become decisive. It is likely that in the future pathological and biochemical data will be demanded, in addition to clinical observation, before case reports of kwashiorkor are accepted.

The later history of the disease will be followed by discussing briefly the evolution of thought along four lines : the relationship to pellagra, the contribution of pathology, the attempts to describe variants, and the evidence which suggested protein malnutrition. This section concludes with a brief account of some of the early European work which has a bearing on the kwashiorkor problem.

1. *The pellagra controversy.* It is now generally agreed that the term pellagra should be restricted to those conditions which have been produced in the body by a deficiency of nicotinic acid, and which, at least in the early stages, can be relieved by the administration of the vitamin. This somewhat dogmatic definition must not exclude from consideration the facts that pellagrins have usually suffered for a long time from multiple deficiencies, including deficiencies of other vitamins of the B complex, which may have led to irreversible changes, and that the protein intake, especially that derived from animal sources, has usually been low. In the

circumstances, it is not to be wondered at that much of the pathology and biochemistry of protein malnutrition may be found in pellagrins.

For many years a dermatosis was considered to be an essential feature of kwashiorkor (Trowell, 1939–40; Williams, 1940–41) and great importance was therefore paid to its resemblance to the dermatosis of pellagra. Considerable uncertainty was felt by those who, working in tropical regions, had seen little or no pellagra in adults, but all those who had had experience of the disease in the southern parts of Africa (Stannus, 1934, 1935, 1936, 1944; Suzman, 1942; Kark, 1943; Gelfand, 1946; Altmann, 1948; Gillman and Gillman, 1951) had no hesitation in regarding the dermatosis of kwashiorkor as pellagrous. Dodd in her chapter on pellagra in children in the book by Harris and Harris (1941) described some illustrations of kwashiorkor as excellent illustrations of pellagra. Castellanos (1935, 1937) in Cuba and Carvalho *et al.* (1945, 1947, 1948) in Brazil also thought the dermatosis was pellagrous. It was the same with those who had seen classical pellagra in Mediterranean countries and also seen kwashiorkor (Hanafy, 1948; Petrides, 1948; Choremis, 1950; Ballabriga, 1950). Few of these writers, however, stressed the several points of distinction (p. 117).

The position adopted by Gillman and Gillman (1945, 1945a, b, c, d, 1946, 1947, 1948a, b, 1951) in their numerous contributions to the study of kwashiorkor seems a little difficult to understand. They demonstrated in great detail that the morbid histology of the dermatosis of African infants suffering from kwashiorkor resembled that of the acute dermal reactions of classical pellagra in African adults, although they could say "The nature, severity and distribution of the lesions would indicate that the disease in infants is in some ways quite different from that in adults" (Gillman and Gillman, 1951). They made a comprehensive study of the changes in the liver and in the other organs, which will be discussed elsewhere, but one fundamental assumption affected the interpretation of their results. They considered they were studying pellagra in infancy: infants having no dermatosis, or in whom the dermatosis had been cured, were cases of "nutritional oedema". Their inability to cure the infantile cases with nicotinic acid was interpreted as proof that pellagra was not merely due to a deficiency of nicotinic acid; the alternative possibility—that their cases of kwashiorkor were not merely pellagra—was not discussed. A recent evaluation of the problem appeared in the report of Brock and Autret (1952), who regarded the dermatosis as allied to that of pellagra but differing in its distribution. It was also decided that the dermatosis was not an essential part of kwashiorkor, and that the latter disease was distinct from pellagra.

In conclusion it should be emphasized that although many have considered that the dermatosis of kwashiorkor is pellagrous, there has usually been a feeling that the two diseases should be separated on grounds such as the natural history, the different age incidence, and the response to therapy (Altmann, 1948). The view held by the present authors is that the contributions of morbid anatomy and clinical pathology have made possible a clear distinction between kwashiorkor and pellagra, although the two diseases may appear together in the same subject, and although recent work has shown a close relationship between the amino acid tryptophan and the vitamin nicotinic acid. More study of the relationship may eventually resolve the divergence of views about the pathogenesis of the skin lesions in kwashiorkor.

2. *The contribution of pathology.* Reference has already been made to the fatty liver which was noticed in the post-mortem examinations of children dying from kwashiorkor. Although it was the one constant and severe change that could be found, its full significance was not appreciated. Up to about 1940, little was known about "lipotrophic factors" (p. 180). Knowledge of the factors grew but slowly and only exerted any effect on the conceptions of nutritional disease of the liver when it was demonstrated that prolonged fatty infiltration of the liver might lead eventually to cirrhosis. A fatty liver might, therefore, be a very serious condition. Even an authority such as Smith (1942–43), who described the fatty liver in kwashiorkor, was inclined to overlook its importance, and having found a similar change in African infants dying of infections, did not apparently consider the possibility that the infants might also have mild kwashiorkor ; the fatty liver was regarded as the expected accompaniment of infective or diarrhoeal conditions. It was almost dismissed as having no significance by Altmann (1948), although he was well aware of work in Johannesburg by Gillman and Gillman.

The assumption that the accumulation of fat in the liver was non-specific, and was merely a terminal event, was successfully challenged by the liver biopsy studies of Gillman and Gillman (1945d), who demonstrated that it was a constant and early change in their cases of kwashiorkor (called by them infantile pellagra).

Two movements were on foot at the same time : one towards a broadening of the definition of the overall clinical picture, the other towards the better understanding of the complex changes detected by morbid anatomy. As clinicians forsook first the " hall-mark " of the dermatosis and later the connection with pellagra they were left with oedema, loose stools and dyspigmentation as the main signs of kwashiorkor. They were fairly sure by now that malnutrition of some kind was involved. Were they observing merely the classical disease of " nutritional oedema ", as some assumed (Gillman and Gillman, 1951), or *Mehlnährschaden* (Altmann, 1948), or a new clinical entity ? Was it indeed a complex syndrome of many deficiencies (Trowell, 1944) with protein, calories, the vitamin B complex and other factors all playing a part, which varied from case to case ? Were there several clinical entities with specific lesions, and consistent changes in morbid anatomy and chemical pathology ? After the liver biopsy studies of Gillman and Gillman (1945d) morbid anatomy seemed to offer great hopes of resolving the whole problem : might not kwashiorkor be fundamentally " fatty liver disease " (Waterlow, 1948a, b), with other defects essentially variable, being merely associated or secondary ? Was there not one organ, and even one specific process, around which the kaleidoscope turned ? Was the organ the liver ?

Waterlow (1948a), in his comprehensive study of infants in the West Indies, took up this aspect of the problem, and was the first to apply tests of liver function. " The babies . . . described were chosen because they presented evidence of liver damage ". They were selected because there was enlargement of the liver, and fatty infiltration found at needle biopsy or at post-mortem, and a low bromosulphthalein clearance. Fifteen cases were collected during a stay of seven months in the British West Indies. None had a characteristic dermatosis and only two had any dyspigmentation of the hair. That the condition remained difficult to define in this part of the world is reflected in a statement of Herlinger (1950), who considered that 20 per cent of the infants in the children's ward of a hospital in Georgetown, British Guiana, showed oedema, dermatosis, and other signs of a condition he called " wet marasmus ".

Carvalho (1947) had found that choline had some lipotrophic effect on the liver in kwashiorkor, but Waterlow could show no such effect of this substance, or of methionine or inositol (p. 183). He demonstrated in one of his cases an atrophy of the acinar cells of the pancreas but did not pursue this line of inquiry.

Davies (1948a) studied biopsy and autopsy material from children, adolescents and adults at Kampala. In subjects under 5 years of age, fat was usually found in the peripheral cells of hepatic lobules, but an atrophy of the acinar cells of the pancreas appeared to be more constant and even to precede the fatty infiltration of the liver. In the later years of adolescence and in adult life the pancreatic changes were present in any case showing oedema, undigested food in the stools and other signs of malnutrition, but the liver might or might not be fatty. In the liver there was, however, a stellate fibrosis in the region of the portal triads. There was a change of emphasis. Kwashiorkor was not merely fatty disease of the liver, but was a condition in which malnutrition was affecting many organs of the body, the most sensitive being those forming zymogen granules for external secretion—pancreas, the salivary glands, the Paneth cells of the small intestine. The fatty changes in the liver were considered to be neither as marked, nor as significant, as the pancreatic atrophy. As other organs began to be examined it was realized that slight but definite degenerative changes were to be found in a large number of them, and the excellence of the comprehensive studies of Bablet and Normet (1937) was realized. Independently of Davies's work a series of papers from Véghelyi (1948a, b; 1950a, b) in Budapest demonstrated pancreatic atrophy and decreased formation of pancreatic enzymes.

Fuller details of the decrease were given by Thompson and Trowell (1952), who also reported that it was rapidly reversed by diets rich in milk protein, with a restoration of the normal acinar structure that could be observed if the organ could be examined at autopsy. The constancy of the pancreatic lesion has been confirmed by Hartz (1949) in Curaçao, Stransky and Dauis-Lawas (1950a, b) and Stransky, Dauis-Lawas and Lawas (1951) in the Philippines, Manson-Bahr (1950–51) in Fiji and Ballabriga (1950) in Barcelona.

Detailed knowledge of the chemical pathology of kwashiorkor has only accumulated in recent years, largely because many hospitals in the Tropics are not equipped for biochemical work. The study of the oedema led to the estimation of the serum proteins, and the discovery of the reduction in the serum albumen. More recently, many other changes have been detected in the serum. Some involve enzyme systems, and it seems possible that alterations in enzyme activity occur in many tissues of the body (p. 168). An extension of the biochemical studies may perhaps satisfy those authors (for example, Kahn, 1952, 1953) who consider that the criteria for the diagnosis of kwashiorkor should be more specific.

It was hoped at first that liver function tests would prove useful in prognosis, but the later results proved disappointing (Meneghello, Niemeyer and Espinosa, 1950) and the changes in morbid histology, as detected at biopsy, have not proved any more helpful in this respect (Altmann, 1950). Enlargement of the liver has proved to be an unreliable criterion in diagnosis (p. 99), and can be misleading. It may appear as a transient phenomenon during treatment (Gomez, Galvan and Muñoz, 1952). Although the enzyme changes just referred to appear to be easily reversible with correct treatment, the extent of recovery and its permanence are at present uncertain. So long as the uncertainty lasts, the ultimate prognosis must be doubtful.

3. *The attempts to describe varying types of kwashiorkor*, *1940–52*. Pathological studies of subjects of various ages by Davies (1948a) suggested that between kwashiorkor in infants and the somewhat similar condition in adults there were certain points of distinction, as well as many points of resemblance. On the clinical side there was the high incidence of the disease among weanlings, and in adults the infrequency of severe dyspigmentation of the skin and hair and the great rarity of the typical dermatosis. In morbid anatomy, although the fatty changes in the liver and the atrophy of the pancreas were so frequently found in infancy, at later ages it was the progressive sclerosis of both organs which was often the outstanding feature. Recent work has made more obvious the necessity to separate the acute and probably reversible changes of childhood from the chronic and less reversible changes seen characteristically at later ages.

Early workers on kwashiorkor in infancy felt the diagnosis should be extended only to those cases which had the dermatosis then regarded as a distinctive " hall-mark ". Eventually, however, it was realized that the dermatosis was not an essential feature, and all cases having unexplained oedema, if it appeared likely to be of nutritional origin, were regarded as possible cases of kwashiorkor.

Despite the many points of difference (p. 117), there was confusion with the hunger oedema of undernutrition, and the term " malignant malnutrition " was suggested to avoid further confusion (Trowell, 1944; Trowell and Muwazi, 1945). Finally, as more and more of the pyramid of malnutrition came into view, it was realized that if a dermatosis characterized its apex, and oedema, diarrhoea and dyspigmentation its middle layers, yet towards the broad base, and mingling with the normal healthy range, there lay a great deal of mild kwashiorkor with less specific signs (Trowell, 1951a). The latter category was accepted only quite slowly, even by paediatricians, who were reluctant to believe that in certain parts of the world the majority of children might be affected.

While the conception of the kwashiorkor pyramid was thus becoming clearer, some details were being studied intensively. Concentration on a single aspect, in mild or severe kwashiorkor, was almost inevitable so long as aetiology remained obscure, but the secret of kwashiorkor will never be revealed so long as the study of the disease consists of isolated attempts to explain individual signs or symptoms.

The gastro-intestinal defect and loose stools attracted attention early in work on the disease, and the segmented appearance of barium in the small intestine (the so-called deficiency bowel pattern) was studied in adults and in children (Brown and Trowell, 1944). Paediatricians of southern Europe and of the Mediterranean countries are still inclined to concentrate on diarrhoea as the outstanding feature in infancy, and to speak of an alimentary dystrophy, or one following gastro-enteritis or dysentery (Shukry, Mahdi and el Gholmy, 1938; Ballabriga, 1950; Choremis, 1950). Others have considered that a condition resembling coeliac disease may commonly follow kwashiorkor, or be a special variety of it (Carvalho *et al.*, 1947) but the condition has not been investigated in the light of modern knowledge of the coeliac syndrome.

Attempts to study cases having no recognizable lesion except the dermatosis have proved unfortunate. There is usually an anaemia accompanying kwashiorkor, but its cause is obscure (Trowell, 1941–42b, 1943; Altmann and Murray, 1948), and cases selected for the severity of the anaemia have seldom thrown much light on kwashiorkor although contributing much to an understanding of the anaemia (Lehmann, 1948, 1949, 1950–51a, b; Woodman, 1950–51).

There is some evidence that the so-called " atrophic " state of kwashiorkor (Altmann, 1948) may constitute a genuine variety. This type of case is described as having little or no oedema, as being thin with a wrinkled skin and a scaphoid abdomen, and as being very refractory to treatment (Janssen and le Roux, 1950a). The condition has also been described in adults (McKenzie, 1940–41). Unfortunately no detailed clinical, pathological or biochemical studies have yet been published on a group of atrophic cases. In the meantime, marasmus due to general undernutrition or dehydration, and an unsuspected complication, seem to be possible explanations. Cases of this kind are very rarely seen in Uganda at the present time (p. 68).

It is reasonable to suggest that a disease so severe as kwashiorkor in infancy might have important sequelae, if it persists for any length of time. The extent to which fibrosis of the pancreas and liver may originate directly in the acute episode of kwashiorkor in infancy is still uncertain ; other organs, such as the parotid and the suprarenal glands, and the metabolism of many substances, such as cholesterol and the steroid hormones, are unlikely to remain unaffected. In a condition so complex, many abnormalities may arise. Malnutrition, if that is the underlying cause, might show in many ways, especially when other processes, toxic or infective, may be present at the same time. The description of new forms of liver disease, found in the tropics, should in the circumstances not occasion too much surprise. Some of them are discussed later (p. 141). Although they too may be new clinical entities, their relationship, if any, to kwashiorkor is quite undecided.

Amongst the many names that have been used as synonyms for kwashiorkor, are several that indicate a belief in a multiple aetiology ; many substances—for instance several vitamins as well as protein—are thought to be simultaneously lacking from the diet. It is argued elsewhere (pp. 62 *et seq.*) that vitamin deficiencies, infections, and variations in diet may modify kwashiorkor, but that all its so-called varieties have much in common. Although there is a great deal that remains to be discovered about kwashiorkor, it is to be hoped that the future will bring simplification, rather than added complexity.

4. *The concept of protein malnutrition.* Even before 1940 there had been a feeling that protein deficiency might play a part in kwashiorkor (Normet, 1926 ; Trowell, 1937) and the beneficial effect of milk had been noted (Payne and Payne, 1927 ; Williams,

1933). When, therefore, the serum albumen was shown to be reduced it was easy to conclude that the oedema of kwashiorkor was of the same nature as nutritional (hunger) oedema and to be accounted for by the lowering of the osmotic pressure of the serum.

The studies of hunger oedema made in Europe and America near the end of the 1939–45 war showed clearly that kwashiorkor and hunger oedema differed in many ways. The latter developed, usually in elderly men and very rarely in children, after a long period of general undernutrition in which the most important deficiency was probably of calories. The visible oedema was generally slight, and the serum proteins were not altered much more than could be accounted for by a hydraemia. There were no marked changes in the liver or in its functions : the appetite was ravenous but gastro-intestinal upsets were uncommon, except in very advanced cases of the kind seen in concentration camps (Helweg-Larsen, Hoffmeyer, Kieler, Thaysen, Thaysen, Thygesen and Wulff, 1952). The response to a full mixed diet was prompt and satisfactory, especially if the patient could lie in bed. All these were points of difference from kwashiorkor, and the possibility of that being a protein deficiency disease became clearer.

Many observers had noted that the diets of children developing kwashiorkor appeared to be deficient in protein (Purcell, 1939 ; Cofiño Ubico and Klée, 1942 ; Russell, 1946 ; Trowell and Muwazi, 1945–46), but few attempts were made to assess the protein quantitatively or qualitatively. The fact that the disease could at times occur in children who were breast-fed, or said to receive some cow's milk (Williams, 1931–32 ; Gelfand, 1946), made it difficult for some to accept the suggestion that the disease was due to protein deficiency. The most comprehensive review of the relationship of diet to kwashiorkor has been provided by Brock and Autret (1952). They agreed with the view that has been accepted in recent years by nearly all investigators : that the disease was due to protein malnutrition.

The poor response made by many cases of kwashiorkor to a diet of whole cow's milk, and the very high mortality rates in cases thus treated was to be a source of misunderstanding and difficulty for many years. The problem of treatment was only resolved when skimmed milk came into use towards the end of the 1939–45 war. Acidified skimmed milk mixtures, sometimes with added milk protein, were used successfully. Later it was realized that skimmed milk powder combined with a suitable carbohydrate to meet the calorie requirements offered one of the best forms of treatment (p. 188). The deficiencies in the pancreatic enzymes explained why cases fared so poorly on whole cow's milk, on nearly all forms of fat and on many forms of carbohydrate. The prompt recovery of pancreatic enzyme activity which followed the taking of a diet containing large amounts of milk protein indicated the value of a rational therapy.

All the advances in knowledge of morbid anatomy and chemical pathology have suggested upsets of protein metabolism. The pancreatic atrophy, the failure of pancreatic secretion, the fatty liver, the disturbances of the serum proteins, the changes in the activity of many enzyme systems, the changes in pigment in the hair and skin, even the anaemia which might be occasionally macrocytic, suggested the same cause and were interpreted most easily in terms of some deficiency of protein intake, of some essential amino acid or of some factor associated with protein.

A note on some European investigations of nutritional disease in children

Substitutes for human milk are mentioned in very early medical literature, but their systematic employment is of comparatively recent date. Desessartz (1760) described the use of the milks of a number of different animals, and also of bread, broken into water and boiled. Underwood (1784) condemned the use of bread in this way, but it was evidently a widespread practice. In Germany by the end of the nineteenth century it had become popular to use cereal gruels, particularly to replace milk when a child had a gastro-intestinal upset, and by 1906 the misuse of the gruels was considered to give rise to a recognizable disease; it was called *Mehlnährschaden* (Czerny and Keller, 1906), a term which is perhaps best translated as " damage by cereal flours ".

Czerny and Keller were apparently trying to bring some order into the confusion surrounding the diagnosis of gastro-intestinal upset in young children, a condition which has been recognized since Parrot's work on " athrepsia " (Parrot, 1877; see also Marfan, 1930) to be of great importance because of the very high mortality. Their approach was influenced by the idea that the upsets were caused by excess, and they described a number of conditions that were supposed to be due to excess of one food or another. *Mehlnährschaden* was thought to be largely due to an excess of flour. Some observations had already been made on the pathology of fatal cases of gastro-intestinal disease in young children, and it was known that in addition to the obvious weight loss there might be alterations in many organs. Thiemich (1896) presented much data about fatty degeneration of the liver, and included notes of a series of 177 cases of enteritis in which this degeneration was found in 76 children aged one to 4 years. Baginsky (1899), who described " atrophic marasmus of nurslings " as a disease well known in Institutions, gave details showing a negative nitrogen balance, and mentioned a marked intestinal atrophy which he thought explained the failure to absorb nutriments ; Arraga and Vinas (1900) and Salomon and Halbron (1908) described alterations of the pancreas ; Bloch (1904) noted considerable changes in the pancreas, including failure of the zymogen granules to take stains, and atrophy of the Paneth cells in the small intestine. Unfortunately, however, it seems fairly certain that much of this pathology was the result of the intercurrent infections which usually caused death, or of conditions such as cystic fibrosis of the pancreas, and other causes of wasting disease, which were more or less obscure at the time.

The first decades of the twentieth century saw a growing interest in the possibility of diseases being due to nutritional deficiencies, and when Nobécourt (1916) discussed gastro-intestinal disease in infants, he spoke of a condition of " hypoalimentation ", due to feeding on vegetable broths or starchy foods, over a long period. If the child was also being breast-fed, the period might be even longer. He thought liver steatosis was exceptional, and mentioned an increase in fibrous tissue in the liver also as a rare finding. The pancreas might be reduced in weight, the ducts slightly sclerotic, and the interstitial tissue thickened ; he said intense interstitial sclerosis had been described by some authors, but was in his opinion not of nutritional origin. Nicolaeff (1923), who investigated children in Kharkov who had died of starvation in the great famine of 1922, pointed out a difference between the livers of oedematous and wasted children ; in the oedematous children there was fatty infiltration, especially in the periphery of the lobules, and in the wasted children the liver cells were atrophic. The pancreas seemed to him unaltered, except for some loss of weight. Stephani (1923), who reported all grades of fattiness of the liver in a series of cases of gastro-intestinal upset, found much fat in two children who had been fed on a diet consisting largely of carbohydrate, and known to be lacking in protein.

In 1928, Czerny and Keller produced the second edition of their book, which included a full description of *Mehlnährschaden*. It was a disease that arose from a one-sided diet, particularly of cereal gruels (this translation has been adopted for the word *Mehlabkochungen*). In the aetiology of the disease local custom might play a part, there being districts where it was usual to give large amounts of sweetened cereal gruels made without milk, but it often happened that the cause was to be found in the over-long continuation of a diet of gruel, introduced originally to stop loose stools. The gruels were usually made without milk, or with very little milk, and the return of loose stools when milk was added was too often regarded as an indication of sensitivity to milk. The condition usually had an insidious onset, and might not be recognized until it was firmly established. The younger the child, the greater was the danger, and the greater the difficulty of bringing about a cure. In the later stages, a new access of diarrhoea was much to be feared, because it was almost always fatal. One especially grave sign was hypertonia of the musculature which reduced the children's mobility and might reach the stage of opisthotonus. Although at first the children might look well, and might increase in weight rapidly on the high-carbohydrate diet, there came a time when the weight gains stopped, the complexion became pale, the tissues lost their turgor, and oedema might appear. It was an extrarenal oedema, and no renal or cardiac cause could be found.

Treatment was always long and difficult. Undiluted cow's milk had been tried but was not recommended for the very young or the very ill; it was thought that its fat was harmful. Human milk, on the other hand, was regarded as the therapeutic food of choice, and as the only food likely to benefit the worst cases. The object of treatment was to redress the imbalance of the cereal diets, and *to supply elements that these diets lacked*: they were not only over-rich in carbohydrates, but were now recognized to be short of almost every other known nutriment. They provided very few calories, they contained very little nitrogen, and they were inadequate in minerals and in vitamins. It was not necessary to abolish cereals entirely from the diet: the gruels could be retained, provided they were fortified; enrichment with whole egg and buttermilk was suggested to increase the protein, cow's milk in increasing quantities would supply fat (some fat was thought to be indispensable), and although *Mehlnährschaden* should not be called an avitaminosis, fruit and vegetable juices, and cod-liver oil, should be given.

A considerable section of Czerny and Keller's book was devoted to an account of the alterations in metabolism in *Mehlnährschaden*, and it was emphasized more than once that it was the deficiencies in the cereal diet that were particularly important. For instance, in the discussion of some negative nitrogen balances, it was said that the gain of nitrogen from the cereal diet was so small and the lack of fat so acute, that the body had to break down its own tissues. Ammonia production was reduced, and the urine volume was abnormally low, in very ill children: the output of urine depended not on the kind of food given but upon the state of the child. The urine might contain an extremely small amount of chloride, and giving sodium chloride might not increase the amount appreciably.

It was realized that not all children were affected equally by the cereal diets, some of them appearing to thrive, and to retain their ability to tolerate fats, whereas others fared very badly. The difference was inexplicable. Gains of weight might be illusory, and due only to water retention, for which sugar might be responsible. The liability of the child with *Mehlnährschaden* to become oedematous was not understood, but the authors had noticed that oedema was likely to appear when sudden loss of fluid (caused, for instance, by diarrhoea) was followed by the ingestion of large amounts of carbohydrate. The atrophic state which was so often reached in chronic gastro-intestinal disease in children was comparatively rare in *Mehlnährschaden*, the reason being that the children were very likely to die quickly of infections, against which they seemed to have no resistance. They might die in this way even after long courses of treatment, which was disheartening. One child apparently died suddenly during treatment.

Among the other changes which had been found in the body, was mentioned fattiness of the liver ; the fat was thought to be derived principally from the fat depots, rather than from the diet, which had frequently been very poor in fat for a long time before the child died, but it had been noted in some cases that the liver was fatty although body fat was not obviously depleted. There might be xerosis, and other eye signs believed to be due to a lack of fat-soluble vitamins, and in xerotic cases there might be pancreatic atrophy.

A few details can be added from Finkelstein (1938). He mentioned a reddish-brown discoloration of the skin, and said that tetany was very common. He also explained the loss of appetite on the grounds of a deficiency of chloride, which, he said, was shown as a failure to produce gastric HCl.

If the reader continues to read this book, he will become aware of many similarities between *Mehlnährschaden* and kwashiorkor. Details of aetiology, pathology and even treatment, apply equally well to both ; the German authors did not describe the alterations in the colour or texture of the hair, or the dermatosis of kwashiorkor, but both of these are known to be subject to great variability. It seems likely that Berlin-trained doctors would have recognized kwashiorkor if they had seen it in tropical countries, and it is possible that accounts of it are buried in the records of observations made in Tanganyika, the Ruanda-Urundi and other territories at one time under German administration. Altmann, who went from Germany to South Africa, said that in its main features the kwashiorkor he saw in South Africa was identical with *Mehlnährschaden* (Altmann, 1950 ; and personal communication, 1948), and Stransky, who had worked in Vienna, also thought that the Philippine disease he was describing resembled it (Stransky and Dauis-Lawas, 1950a). It was obvious during the years that one of the present writers spent in Germany after the recent war, that the German paediatricians had not forgotten *Mehlnährschaden*, but the disease does not appear to have been described in Germany as a consequence of the war. It seems, however, that it occurred, and may still be occurring, in certain parts of Italy (Frontali, 1953), where it is known as *distrofia da farine* or *distrofia di carboidrati*. Comparing this disease with kwashiorkor, Frontali says that in the *distrofia* hyperpigmentation of the skin has sometimes been seen, and alterations in the texture of the hair. It is possible that these manifestations also occurred in classical *Mehlnährschaden* in Germany, but were missed or thought to be of no special significance. Frontali, like Czerny and Keller, stressed the association of his disease with vitamin deficiencies ; keratomalacia and other eye signs, rickets and scurvy, were all to be found.

In a most interesting paper entitled *Die Eiweissmangeldystrophie*, the Swiss authors Fanconi and Prader (1950), described the effects of a shortage of dietary protein in a series of 7 young children. Many of the points they discussed, such as the lack of a simple explanation for the cause of the oedema, the low levels of alkaline phosphatase and cholesterol in the serum, and the urgency of the need for protein in therapy, suggested a close relationship to kwashiorkor. Their choice of title is significant, because they were fully aware of *Mehlnährschaden*, but obviously thought *Eiweissmangeldystrophie* (protein-shortage dystrophy) more comprehensive and exact. A concise account of the similarity between *Mehlnährschaden* and kwashiorkor is given in the textbook on the feeding of children by Meyer and Nassau (1953).

PART III

KWASHIORKOR IN CHILDREN

THE NATURAL HISTORY OF THE DISEASE

1. The age incidence

The data given by a number of authors concerning the age of 1141 children suffering from kwashiorkor are given in Table 1. It is well known that in poorly developed communities, where there is no machinery for the registration of births, ages are often stated inexactly. The data must therefore be approximate, but they undoubtedly describe the age incidence reasonably well.

TABLE 1

Age distribution of children reported to have kwashiorkor
(From various sources)

Age	Number of cases	Percentage of total
2–6 months	21	2
6–12 ,,	174	15
1–2 years	516	45
2–3 ,,	271	24
3–4 ,,	80	7
4–5 ,,	53	5
5–9 ,,	24	2
9–20 ,,	2	0·2
Total	1141	100

The recorded age was almost always that at which the child was brought to hospital for treatment, and the true age of the child at the onset of the disease has seldom been stated. As there is always a more or less prolonged period during which the child's health has deteriorated, it is difficult even for intelligent mothers to state more than the duration of the recent phase of serious illness. A number of other factors also may have influenced the figures for the various age groups. There may have been a deliberate selection of a homogeneous series of cases, such as that collected at Kampala for the investigation of serum biochemistry (p. 207). Other cases may have been selected only from child welfare clinics, or have been studied by paediatricians who might see few cases in adolescents, and none in adults. Exigencies of space in hospital, or the reluctance of mothers to leave children there below a certain age, or difficulties in transport, may also have been responsible. Nevertheless, the evidence suggests that the onset of the disease is very often shortly after weaning, a view expressed by many writers (among them Payne and Payne, 1927; Hughes, 1945–46; Russell, 1946; Waterlow, 1948a; Delon, 1950a, b). Kwashiorkor may appear in infants who are still being breast-fed (Oomen, 1953), but such children have probably been receiving only a little breast milk in recent weeks.

The occurrence of kwashiorkor in children under the age of one year seems to demand rather special circumstances. Altmann (1948) described one case of a child 3 months old who had never been breast-fed. An early failure of lactation in the mothers, combined with the almost complete absence of cow's milk, was probably the reason underlying the appearance of many cases of the disease among very young children during the siege of Budapest, where half the cases were under 6 months old (Véghelyi, 1950a); these cases were not included in Table 1. Stott (1948) reported several cases under 6 months of age, among Kikuyu infants in Kenya; he also described how shortly after the birth, especially if the breast-milk was declining, the mothers chewed burnt banana and other foods, which they then fed forcibly, mouth to mouth, into their unfortunate children.

It is probable that the onset of kwashiorkor may depend in other ways on the mother. She may bear the permanent disabilities of past episodes of malnutrition, which in one way or another reduce her efficiency. By analogy with some animal experiments (Dean and Schwartz, to be published), it seems possible that the adequacy of the diet during pregnancy and lactation, particularly in regard to its richness in protein and vitamin B_{12}, may decide whether or not the child is attacked, or at least the age at which the disease appears. If the mother's milk is deficient in an important amino acid, and especially if that deficiency is of methionine, as in the reports of Auffret and Tanguy (1949), it is possible that the child may suffer acutely and at an early age, and the more so if the diet offered as a supplement to the diminishing breast milk is also deficient in that amino acid.

In the absence of complete records for incidence, it is impossible to be certain whether or not the average age at which kwashiorkor appears is different in different places. The Central American paediatricians with whom this question was discussed (by R. F. A. D.)

said that the average age of their cases was greater than that found in Africa: it was nearer to four years than two. If this difference is real, it should be investigated to find out if it depends on the basic diet, on occasional supplements to that diet, or on some other factor. In Costa Rica (Peña Chavarría, 1953, personal communication) there were formerly many examples of the disease to be found in school children, six years old or more. In recent years, however, there has been a decline in the number of these cases, and it is thought that the decline is due to the starting of school feeding programmes.

The acceleration of growth which occurs at puberty, or just before, might be expected to cause a rise in the incidence of kwashiorkor. The disease is, however, very rare then, and although a few cases have been described (for instance, by Dricot, Beheyt and Charles, 1951) one of the present writers (H. C. T.) can recall only one between 12 and 18 years of age in his twenty-three years' experience. The reason may be that the protein requirements per unit of body weight do not rise at puberty, or that there is an increase in appetite which satisfies the need for more calories and at the same time raises the protein intake. The correct explanation will not be known until a proper study of growth in children on low-protein diets has been carried out, with observations of the results of giving additional protein.

2. The sex incidence

Few papers give the sex of the children described. A total of 194 boys and 174 girls was recorded by Altmann (1948), Gillman and Gillman (1945a), Trowell (1937), Waterlow (1948a) and Stott (1948). The slight preponderance of boys is inconclusive. In a small series of Kampala children there was a similar excess of boys and also a suggestion that the average age of the girls was a little greater than that of the boys (Trowell, Davies and Dean, 1952). Many further records must be collected before this point can be regarded as established, but it is a well-known fact that undernutrition nearly always affects boys more easily than girls, and it is possible that girls might resist more successfully the onset of kwashiorkor.

3. The social background

There are many references in the literature to the fact that kwashiorkor is far commoner among poor communities and among the most depressed social classes. No one has recorded a contrary view. Even those who have doubted whether kwashiorkor was a nutritional disease have not found cases in the more wealthy families, unless the feeding was exceptionally poor. In children of such families the disease occurred at a later age than is usual (Achar, 1950). Normet (1926) in Indo-China considered that *Bouffissure d'Annam* occurred only among the poorest labourers, and Payne and Payne (1927) found their cases of " oedema disease of Haiti " only among children of the lower-wage groups. In the Caribbean area and in Central and South America the relationship of kwashiorkor to poverty has been stressed, as well as the frequency of the disease among orphans, neglected children and those having a disrupted family life (Castellanos, 1935, 1937 ; Vilá and Artola, 1936 ; Cofiño Ubico and Klée, 1942 ; Waterlow, 1948a). In tropical Africa, until recently, there was less stratification of society into rich and poor, the large majority of the people being peasant cultivators. Under such conditions, the incidence of kwashiorkor may not vary between the different social classes, but may vary much from one part of the country to another, depending largely on agricultural and veterinary practice and also upon social customs, especially those which prevail at the time of weaning.

In all rural areas the incidence of kwashiorkor depends more on the type of foods grown than on the amount of monetary income. The need to buy food is for many Africans quite unknown, or a comparatively recent innovation and restricted to certain articles like meat and fish. In the larger towns of West and South Africa, in the older countries of Asia, in some parts of the Mediterranean, and in Central and South America, matters are very different and the incidence of kwashiorkor must reflect the ability to purchase foods rich in protein. In the broadest sense of the word there is usually a connection between poverty and kwashiorkor. Donnelly's (1951) translation of a popular saying is revealing : " When the parents are poor the infant cannot get any proper substitute for its mother's milk, and so gets the sickness."

The relationship of kwashiorkor to over-population is less obvious ; if the over-population produces poverty, as it almost always does, there is an indirect connection. In towns excessive population, especially if coupled with under-employment, reduces the amount received in wages and therefore the amount of money available for the purchase of foods, especially those rich in protein, which are notoriously expensive. If over-population occurs in rural areas the amount of land which can be devoted to cattle is decreased, with shortages of meat and milk, and as pressure increases it becomes a matter of the greatest necessity to plant crops yielding the largest number of calories per unit of land simply to avoid famine (Table 20, p. 244). In temperate regions a cereal such as wheat which contains a fair amount of protein is usually the basic crop, but in the tropics the foods which yield the largest number of calories per unit of land are low in their protein content (p. 239). In temperate regions over-population may produce general undernutrition and eventually hunger oedema ; in tropical regions it may produce kwashiorkor in children and protein deficiency states in adults.

In Asia kwashiorkor certainly reflects over-population and poverty (Achar, 1950 ; Stransky and Dauis-Lawas, 1950a). In Africa, and in many other parts of the world, the problem is being complicated nowadays by the movement of the population from country parts to the towns, by the breakdown of the old patterns of family life, and by the changing social customs of the people. On the other hand, kwashiorkor is uncommon as a severe disease in some undeveloped areas of Africa, where family life is stable, where cash crops are not much grown, and where the land is suitable for mixed farming and animals can be kept usefully.

The "deprived" child

In recent years, various authors, amongst them Bowlby (1952), have drawn attention to the effects that may be produced in children by deprivation of mother love and care. The effects are most marked in children who are abandoned before they are three years old, and they are not only psychological—the child becomes "difficult", asocial, silent, unresponsive, and unteachable—but physical : probably as a result of a failure of the ordinary eagerness of appetite, growth is poor and a bad posture enhances the miserable appearance. In many places where kwashiorkor is found, it is customary for children to remain in almost constant physical contact with their mothers for the first year of their lives, or even longer. They are carried on her back wherever she goes, held on her knee when she sits down, and sleep by her side, and if they are frightened or upset, they turn at once to her breast, which represents security and comfort, although it may have ceased many months ago to provide

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nourishment. Suddenly, all this is changed: for one of a variety of reasons, which include the beginning of a new pregnancy, the child is sent away from his parents, usually to entirely new and strange surroundings. He may be fortunate in finding there an adequate substitute for his mother—perhaps a woman whose child has recently died, or a childless woman who can devote herself to his care; or he may have to take his chance of affection in a family where he is an interloper. The effects are discussed by Carothers (1953), but their full implications are unknown. On the basis of European experience, some psychological trauma would seem to be inevitable, but in a culture where the separation is normal, some compensatory mechanism may have been evolved, and the child may not suffer to the expected extent. At Kampala, many of the children who are admitted to hospital for severe kwashiorkor are brought by relatives, other than their parents, who have been responsible for their care and are therefore responsible for their condition: it has not so far been noticed, however, that such children are in a worse state than those who have been always with their mothers, and the whole question of the effects of "deprivation" on the African child obviously awaits investigation. As a factor in the aetiology of kwashiorkor it is at present an uncertain quantity.

4. Geographical and racial distribution

The apparent extent of the geographical distribution of kwashiorkor (see p. 1) has been influenced largely by imperfections in recognition of the serious cases and the difficulty in defining the signs of a mild attack. Until these two obstacles have been overcome it is impossible to know exactly the geographical distribution and the incidence. It would be unwise to assume, merely because kwashiorkor has not yet been reported from such countries as Liberia, Ethiopia, Madagascar or the Spanish or Portuguese African territories, that no cases are to be found there. It is more likely that no one has looked carefully for the disease or ventured to report it. It is probable that in all tropical countries there are certain districts in which the disease is common in a more or less serious form, and even larger areas in which it is to be found in minor degrees. The incidence in various areas and among various groups will usually reflect economic, social and agricultural patterns, based on rainfall, the soil, the temperature and the amount of available land.

In the more populated areas of West Africa, in North Africa, South Africa, in Egypt and the Middle East, kwashiorkor has been most frequently reported in the large towns (Hughes, 1945–46; Hanafy, 1947; Delon, 1950a, b; Gillman and Gillman, 1951), but it is impossible at present to be certain that the incidence is greater in the towns than in the surrounding countryside.

Very few cases have been noticed in the temperate region of any continent and it is likely that some unusual circumstance is always responsible. In North America no cases have been reported from Canada or Alaska; in the United States Lewis (1926) described a possible case in a coloured infant, and gave an excellent illustration of the characteristic dermatosis on the trunk. The skin changes were regarded as pellagrous by those who had seen much classical pellagra in adult American negroes. Dr. Grace Goldsmith (1953, personal communication) found three children who showed signs of kwashiorkor in a poor and numerous negro family living on a Louisiana plantation. The father's earnings were very small because he was not regularly employed, and local food prices were exceptionally high. Other reports of oedema and diarrhoea in young children in the United States are difficult to evaluate, and cannot be called kwashiorkor. Most countries of Central and South America appear to have the disease. Some parts of the Argentine and Uruguay, which are in temperate regions and have meat and milk as basic articles of diet, may be exceptions.[1]

In Europe the position is becoming clear. *Mehlnährschaden* (p. 41), which may be identical with kwashiorkor, occurred in certain parts of Central Europe early in the present century and there are still cases of " starchy food dystrophy " in Italy (Frontali, 1953), and probably in other southern European countries. Kwashiorkor became extremely common among the children who lived

[1] For various reasons, some of the South American literature which probably has relevance to the problems of kwashiorkor has not been available to the present authors. The reader who is interested will find a remarkably full bibliography in the monograph by Meneghello (1949). Among the papers cited there, but which have not been read in the originals, are those by Franco (1939), Delgado (1945) and Zubillaga and Barrera (1945), who have, it seems, described cases in Chile and Venezuela. Stransky and Dauis-Lawas (1950a) refer to cases in Colombia described by Hernando-Ordoñez (1946) which, they say, were certainly kwashiorkor. An account of the disease in Brazil, by Dr. J. C. Waterlow and Dr. A. Vergara, is due for publication in the near future by the World Health Organization.

through the siege of Budapest and were deprived of all milk (Véghelyi, 1948a, b, 1950a), and among children in Greece whose diets were similarly impoverished (Petrides, 1948). Cases appeared among the refugee children investigated by Tiling (1947) who were brought to Hamburg after a long and difficult journey, during which they were said to have had very poor food. Isolated cases of kwashiorkor have been recorded in France, in infants given very abnormal diets. Thus Ribadieu-Dumas, Mathieu and Lévy (1927) gave details of a young child who had attacks of gastro-enteritis starting at the age of 16 months, which were probably of allergic origin, and subsequently was fed almost exclusively on a starchy diet. He passed loose stools which contained undigested food, developed oedema and a dermatosis which was considered to be eczematous, and was cured by a diet rich in protein. Levesque and Hardouin (1953) had under their care in Paris two children whose parents were from North Africa, and who had a dysenteric illness for which no infective cause could be found. It was finally decided that the origin of the illness had been an attack of diarrhoea, which may itself have been caused by undernutrition : the attack had been treated with a light diet that included fruits and other foods likely to have produced more upset. The fruit diet was replaced by a diet, supposedly bland, that contained very little protein, and the children became very ill. It was realized that their condition resembled kwashiorkor.

Probable cases have been described in Spain by Ballabriga (1950) and Torres Marty (1951) and in Greece by Choremis (1950). No cases have been traced in the paediatric literature of Great Britain, Norway, Sweden, Finland, Denmark or Belgium.

In Asia kwashiorkor has been recognized for many years as " nutritional oedema " or " nutritional oedema syndrome " and is probably widespread. The dermatosis is seldom severe, and when it occurs is less pigmented in sallow-skinned Asians than in dark-skinned Africans (Oomen, 1951). It appears that it often escaped recognition (Nicholls, 1946). In recent years many cases have been reported in India (see p. 5), and well-identified cases have recently been described in Ceylon (Jayasekera, de Mel and Cullumbine, 1951). Some of those cases described by Chen (1942) in China were strongly suggestive of kwashiorkor, and Stransky (1950) referred to cases in Canton. Japan has recently reported a large series (Arakawa, Wada and Takahashi, 1951). The disease appears to be widespread in Indonesia and certain of the islands of the Pacific (Oomen, 1950a, b, 1951, 1953; Manson-Bahr, 1952). No cases have been described in Australia or New Zealand.

5. The influence of climate and season

In certain parts of the world kwashiorkor appears to have a seasonal incidence, but in other areas cases occur fairly regularly throughout the entire year. Seasonal changes of climate are said to affect the incidence of kwashiorkor in Tunis; one writer (Didier, 1953a, b) quotes the classical belief that the period between summer and winter has a malign influence on nutritional functions, and other writers (Caruana, Hamza and Ghileb, 1953) point out that in late summer gastro-intestinal upsets are very common in children, and are often treated by removing milk, and other valuable foods, from the diets. In Central America (Autret and Behar, 1954) more cases are seen in hot weather than in cold, and it is believed that summer diarrhoea is responsible; it is also thought that more cases occur throughout the year in warm and low districts than in the mountainous ones. Otherwise, climate influences kwashiorkor mostly through its effects on the food supply: in Costa Rica a rise in incidence at the end of the rainy season is said to be due to the roads becoming impassable, so that food cannot be taken along them: elsewhere it determines the pattern of agriculture, and the abundance or lack of foods that may be protective. The absence or rarity of kwashiorkor in the temperate regions is probably due to the consumption of a fair amount of protein in cereals and milk.

Climate is certainly a factor in determining the types of food grown in tropical Africa. There are few parts where rice can be grown, and if the rainfall and humidity are high it is difficult to grow other cereals or to store any forms of food, including leguminous crops, such as beans and peas. Cattle diseases abound. There is much grass of a kind, but it is tall and coarse and so far very little use has been made of it. Within the moister areas of the tropical belt there may normally be little seasonal change in the foods eaten, but the crops may be destroyed by too much rain, and if there is a drought and a famine (Cochaux, 1937) cassava may be resorted to (Pieraerts, 1942). Kwashiorkor becomes more common after such calamities. In tropical regions changes in the food supply become more accentuated in mountainous areas. Stott (1948), who worked among the foothills of Mount Kenya, noted that the incidence of kwashiorkor was low from April to August, a period during which the millet crop planted in the previous September was eaten. In August, maize ripened and was the principal cereal in the diet ; the incidence of kwashiorkor remained low so long as the maize lasted, but rose again in November or December, when it was becoming exhausted. A fall in the incidence occurred in January and February, and was attributed to a harvest of beans, but in March, when that crop was in turn finished, there was the heaviest incidence of kwashiorkor. Only a short distance away Clark (1951a) noted that there was a period of food shortage from January to March, and that the incidence of kwashiorkor was at its highest from April to June. Where there is much seasonal variation of food in the Tropics the most difficult period usually occurs soon after a rainy season has begun, and continues until the crops are harvested. Strangers may have difficulty in realizing that the rainy season is the time of greatest food shortage. The heaviest incidence of kwashiorkor invariably occurs when food has been scarce for some weeks (Doucet, 1946).

In the sub-tropical regions there is usually only one rainy season, and it is during this period and while the new cereal crops are growing that kwashiorkor may be most severe. Its occurrence during the rainy season in Rhodesia led Gelfand (1946) to suggest that the disease was not nutritional in origin. Fresh food may be available during the rains to relieve certain vitamin deficiencies, but it is not until the new crops are harvested that the shortages of protein and calories, which arose during the previous dry season, are overcome. In Johannesburg the incidence of kwashiorkor (infantile pellagra) was maximal in the southern midsummer months of December and January. Gillman and Gillman (1945a) considered that this confirmed the relationship to classical pellagra in adults, since the incidence of the latter disease was maximal at the same time. More information is needed concerning seasonal fluctuations in food supply in urban and rural areas in South Africa before these facts can be evaluated. It seems to be well established that exposure to sun, cold winds, and changes of temperature may provoke the dermal reactions of classical pellagra, and the possibility that such factors may influence the onset of the dermatosis of kwashiorkor cannot be dismissed. Reports from Central and South Africa suggest that the dermatosis of kwashiorkor is more frequent and more extensive if the weather has been severe and that the connection is most obvious where maize is the staple diet. If kwashiorkor is diagnosed only when the dermatosis is seen there might well appear to be an increased incidence of kwashiorkor during the spring and early summer months (Gillman and Gillman, 1951).

6. The dietary background

Almost everyone who has investigated kwashiorkor has come to the conclusion that diet plays a large part in its aetiology, and in recent years opinion has become more definite that the most important dietary factor involved is protein.

Since the disease is so rare in the first months of life (Table 1, p. 47) it seems probable that breast milk is an excellent protective agent. As long as its quantity—and presumably its quality—is sufficient, kwashiorkor does not occur. Breast-fed babies reported to have the disease have always been markedly underweight and almost always obtaining unsuitable supplementary vegetarian foods; the breast milk was obviously not adequate.

The property of breast milk which makes it so obviously advantageous in the prevention of kwashiorkor is not easy to distinguish. It has been suggested by Gyorgy (1952, personal communication) that the milk contains substances having a protein-sparing quality, and if that is so their detection and isolation are matters of prime importance for the understanding of kwashiorkor. It is conceivable that a vitamin, a phosphoric compound, or an enzyme may one day prove to be of supreme value, but at the present time the most obvious possibility is the milk protein. Only about 8 per cent of the calories provided by breast milk are in the form of protein, but the milk is such an efficient food that this percentage cannot be used as an index of the amount of protein needed when a mixed diet is being taken. The protein requirements of a child at the beginning of his second year of life, when he must always be on a mixed diet, are at their maximum in relation to body weight; thereafter they will decline, and the decline will follow the natural decrease in the rate of growth. The high incidence of kwashiorkor in the second year is, it seems, almost certainly due to the high protein requirements at that time. The food available is taken in amounts that satisfy hunger, and if the food contains little protein, kwashiorkor may ensue; if it contains more protein, kwashiorkor may be prevented. The ratio of protein calories to total calories in the diet is obviously important, and it is a lamentable fact that for many of the foods grown extensively in the Tropics, the ratio is low (p. 239).

Cow's milk is a food in which the ratio is high, and that may be one reason why studies of the incidence of kwashiorkor nearly always lead to the same conclusion : that the incidence is never great if the diet includes much milk. Among pastoral tribes there is little or no kwashiorkor, at least if the children receive milk (Brock and Autret, 1952), and in Uganda none has been found among the Hima tribe, who live entirely on milk and other animal products (Smith, 1952). In the province of Guanacasta in Costa Rica there is much poverty, and the general economic position is worse than in the rest of the country. Nevertheless, the " multiple-deficiency syndrome " is very rare in the province, the reason being that cows are kept and milk and cheese are common articles of diet (Autret and Behar, 1954). Bergouniou (1952) said that kwashiorkor could be found in the vicinity of Dakar, but never in children whose diet included cow's milk, and in the course of a careful examination of the diets of Kampala children, carried out by a well-trained African research assistant, it was noticed that the poorest families —amongst whom kwashiorkor seemed to occur with the greatest frequency—bought no milk at all, or only enough to flavour their tea occasionally : on the other hand, all families, however poor, bought meat or fish once or twice a week. In other places, where fish is a considerable part of the diet of the child, it may be protective against kwashiorkor. The absence of kwashiorkor in coastal districts of Central America and West Africa is attributed to the consumption of fish (Autret, 1953, personal communication), and the opportunities for obtaining fish, either fresh or dried, seemed to one of us (R. F. A. D.) a possible reason for a better state of nutrition in children in some of the coastal districts of Kenya than in the hinterland.

The amino acid composition of nearly all animal proteins is much the same, and all animal proteins supply vitamin B_{12} (p. 238). Nevertheless, meat and fish are probably of less value to the child threatened with kwashiorkor than milk would be. The reason lies partly, in Uganda at least, in the dietary habits of the people. The greater part of the day's food is taken by the adults at only one or two cooked meals ; the child may be given snacks at other times, but the snacks are usually pieces of left-over food, such as cooked banana (plantains) or sweet potato. The meat or fish is only eaten at the cooked meal. A common way of using the meat or fish is to make a sauce of it, and to press boluses of the more bulky food into the sauce—an operation which needs more dexterity than the small child usually possesses.

Cow's milk, like breast milk, undoubtedly has special virtues, which are discussed elsewhere (p. 199). Where little or none of it is available much depends on the quality of the rest of the diet given to the child after weaning. If the diet includes some good cereals, and plenty of beans or peas, all may be fairly well even if the supply of animal protein is restricted : if the staple articles are bananas, sweet potatoes, yams or cassava, kwashiorkor is likely to flourish.

Many of the foods used as a weaning diet are unsuitable for that purpose not only because they have insufficient protein but for other reasons as well. Many are extremely bulky in the forms in which they are eaten, and the sheer size of a meal that might have an adequate caloric value would defeat the most willing appetite (Trowell and Muwazi, 1945). Some of the foods are difficult to digest, either because they are hard and cannot be softened even by prolonged cooking, or because they contain much fat ; groundnuts (peanuts), in some ways a valuable food, combine both these disadvantages. The amount of fibrous matter in other foods may be very high, as it is in sweet potatoes and plantains, and may present a bar to the effective utilization of nitrogen and other nutrients.

Lack of protein does not by itself cause kwashiorkor. It is important to distinguish clearly between dietary conditions producing kwashiorkor and those producing 'undernutrition on a balanced diet'. In the latter there is a simultaneous reduction of all food elements and it is the reduced caloric intake that threatens life and will soon end it. The need for calories first causes the disappearance of body fat : at the end protoplasm is surrendered in a desperate last attempt to supply calories, and all the organs atrophy in an order which seems to be related to their truly vital importance. In kwashiorkor it is the shortage of protein, and possibly of factors allied to protein, that is of chief importance. In the initial stages, before the anorexia develops, there may even have been in some cases a fairly high calorie intake.

It is probable that the usual cause of kwashiorkor in young children is the prolonged ingestion of diets having a low protein/calorie ratio, but this broad generalization is subject to some modifications. For instance, it is generally agreed that animal protein is superior to vegetable protein in the prevention of kwashiorkor; this may be due to the fact that the former usually contains more of certain amino acids, especially methionine and lysine, which are probably required in large amounts for growth, and which cannot be synthesized in the body. It is also possible that substances normally found in association with some proteins may play a part: these substances may "spare" protein, or enhance the use of one or other of the amino acids of the protein, or prevent some of the changes in organs such as the liver (p. 180).

A diet containing a low protein/calorie ratio may normally be taken in amounts great enough to satisfy hunger, but if the amount of the diet is reduced for any reason, the shortage of protein is accentuated. The point is most important but is seldom realized: when such a diet is even moderately reduced, the level of intake of protein may fall dangerously low although the level of intake of calories becomes no more than slightly insufficient. It is obvious that kwashiorkor might be made worse. There are reasons for believing that this sequence of events actually occurs. Clinical observations on children with severe kwashiorkor suggest that they have eaten for many months monotonous diets with a low protein/calorie ratio; the diets have, incidentally, contained very little animal protein. The food has been offered in amounts adequate, or nearly adequate, to satisfy hunger. At a certain stage in the disease-process the appetite begins to decrease, and consumption lessens.

The alteration in appetite probably occurs at an earlier stage than is generally recognized, and may be an essential feature of all cases of mild kwashiorkor (p. 110). Some children seem to be able to adjust themselves to the lower level of intake; it is possible that in their diets the protein/calorie ratio is only slightly sub-normal, or that by reducing their growth rate they reach a state of equilibrium. Other children become more seriously ill, for reasons that are not clear. Possibly their diets have a lower protein/calorie ratio, or contain less of certain essential amino acids or associated protein factors. They may be children with abnormally high protein requirements, due to some unexplained personal peculiarity of the kind which is known to cause large variations in the caloric requirements of different individuals. Possibly some infection increases the protein requirements (p. 65); appetite may be further reduced as an effect of damage to organs such as the pancreas or liver, and even if the absorption of food from the intestine is not at first greatly impaired, its utilization may be imperfect because of the failure of intracellular enzyme systems. Protein deficiency continues to be dominant; calories are also in short supply, but if the retention of subcutaneous fat is a reliable index, the caloric deficiency is not the most serious one. (It is of course, conceivable that the fat cannot be mobilized because some essential mechanism has failed, but that awaits investigation.)

In the last stages, all features of the disease-process become intensified as the intake of food is reduced by the mounting anorexia. Death may result from a mixture of protein deficiency and caloric deficiency. If the protein element is more important, the picture will be that of kwashiorkor to the end; if for some reason the caloric element predominates, the final state may be one of starvation.

Some quantitative data. No exact measurements of the home diets of children who have developed severe kwashiorkor have yet been possible, but a little more is known about the diets of children believed to have mild kwashiorkor (p. 110). Moen, whose results are given by Autret and Behar (1954), measured the food taken by 5 children in Costa Rica who showed signs of "multiple-deficiency syndrome"; they were all from poor and numerous families. Their ages were 2½, 3, 3¼, 4 and 5 years, and their respective daily calorie intakes were 731, 444, 533, 1,390 and 650. The total protein ranged from 13 to 43 g.; two children had no animal protein at all, in two others the animal protein was one-nineteenth and one-eighth of the total, and in the fifth child the intake of animal protein was 11 g. but the total was only 15 g. A survey was arranged (Holmes, 1953, private communication) amongst children attending a child welfare clinic near Kampala, in a district where about 40 per cent of the children show signs suggestive of the mild disease. Twelve children were studied, 6 of them from poor peasant homes, and 6 from homes where the parents were more educated, and a little more wealthy. In both groups cooked bananas (plantains), sweet potatoes and groundnuts supplied most of the calories, and all the children were apparently given enough food to satisfy hunger. The peasant children, whose average age was about 28 months, took approximately 750 calories daily, to which total protein contributed 90 (12 per cent) and animal protein 40 (5 per cent); the other children, whose average age was 23 months, took 1125 calories, 145 (13 per cent) from total protein and 65 (6 per cent) from animal protein. British children aged 18 and 30 months respectively who were studied by Widdowson (1947) took 1150 and 1400 calories, 165 and 185 (14 and 13 per cent) from total protein, and 115 and 120 (10 and 9 per cent) from animal protein. The low percentage of animal protein in the diets of both groups of African children, and the very low calorie intakes of the peasant children, are perhaps the most remarkable features in this comparison. The peasant children were probably smaller than the British children of the same age, but their intakes per kilogram of body weight must have been much less. They may have had an unrecognized anorexia—a slight degree of that state which is so marked in acute kwashiorkor. Whatever the cause, their intake of protein must have been dangerously low.

7. The part played by infections

Infections raise many problems in relation to kwashiorkor, but one of the most important is whether or not they play any part in causation. Much more is known about the fully developed disease than about the incipient state, and it may not be unreasonable to start with a discussion of some clinical observations.

It is the common opinion that children in whom kwashiorkor is established contract infections easily. This was the clinical impression of almost all the early workers, but it should be remembered that their cases were poorly treated and remained anorexic and oedematous for long periods. Further, when any infection occurred there were no specific methods of treatment by antibiotics or sulphonamides, and broncho-pneumonia carried off most of the children (Trowell, 1937).

There is no definite proof that kwashiorkor predisposes to infection. No statistical data are available, and at Kampala the infrequency, and not the frequency, of cross infections amongst the children in hospital with kwashiorkor has been noticeable in recent years. These children are, however, always under treatment with a good diet, which may itself be to some extent prophylactic. The true relation to infection will not be known until children with and without mild or severe kwashiorkor have been observed in their own homes, or under controlled conditions such as might be established in an orphanage.

For the present, the only source of information is the state of the children when they are admitted to hospital as compared with that of children admitted for diseases other than kwashiorkor. At Kampala the children's ward is shared by medical and surgical cases, and the latter provide a useful clinical comparison. The children suffering from kwashiorkor seem to have more upper respiratory troubles, and are more liable to gastro-intestinal upsets, but do not have more malaria. It is not possible to go beyond these vague statements, which are unfortunately not supportable by adequate figures for the incidence of the various infections. The frequency of terminal infections noticed at autopsy was probably the origin of the idea that all severe cases of kwashiorkor must also have an infection. Cases in which it is impossible to discover any infection, bacteriological or parasitic, likely to affect health, are not rare in Kampala, and discussions with paediatricians from South and West Africa, Mexico, Central America and India have made it quite clear that uninfected cases are always to be found.

Even the most careful history-taking usually fails to provide any trustworthy evidence for the relation between an infection and the onset of kwashiorkor. Purcell's (1939) observations of the connection between the dermatosis and measles (p. 24) has, however, received some confirmation at Kampala, where Thompson (1952; personal communication) noticed an increase in severity of the skin lesions at a time when an epidemic was active. In Africa it is only in exceptional circumstances where the propaganda has been good, and the education of the mothers in matters of health has been sufficiently intensive, that children are brought to any hospital because they are suffering from kwashiorkor. In the more backward areas they are brought to hospital largely because they have acquired some well-recognized infection. On the shores of Lake Kivu, expeditions into the villages were necessary to convince mothers that their children, many of whom were in fact suffering from advanced kwashiorkor, had an illness which could be treated in hospital. The position was complicated in this district as in many other areas in Africa, by a reluctance of the mothers to admit the possession of children who had this particular illness; it was apparently considered in some way shameful (Demaeyer, 1952, personal communication). In this connection the relationship of kwashiorkor to the stigma of a second pregnancy should be remembered (p. 10). At Kampala, although it has for some time been exceptional for many children admitted with kwashiorkor to die, and although the signs of the disease are well known, it is only in recent years that the disease, and not a complication, has brought the child to hospital. Once it has been demonstrated that kwashiorkor can be cured, the hospital ward may be full of cases.

Something of the relationship of kwashiorkor to infection may perhaps be inferred from the complications seen in established cases. Purcell (1939) noted frequently a moist rash around the external auditory meatus, but this was possibly part of the dermatosis, rather than a sign of an infection of the ear. Many authors have remarked on the frequency of bronchitis and pneumonia. In some countries, including South Africa and the Philippines, a primary tuberculous complex seems to be common, and may not be suspected until the tuberculous process has become disseminated through both lungs. Jelliffe (1952) commented on the frequency and severity of cancrum oris in Nigeria.

Although a failure of digestion must be considered as an important part of advanced kwashiorkor, diarrhoea from an infection may also occur. The number of flagellates of all kinds in the stools is sometimes so great as to raise fears that they are pathogenic (Trowell and Muwazi, 1945–46), but the flagellates often decrease as soon as correct dietary treatment is established. A true dysentery of the bacillary kind and amoebic dysentery are rare complications at Kampala but commoner in some Asian countries (Oomen, 1951 ; Achar and Benjamin, 1953).

Urinary infections, which can easily be missed because of the inconstant slight albuminuria (p. 105), sometimes occur. Any of the skin lesions may become septic, but when their number and extent are borne in mind, it usually appears remarkable that severe infection is not more common.

It has been noticed at Kampala that most infections superimposed on kwashiorkor do not give rise to more than a slight alteration in temperature, or more than a feeble leucocytosis. Reports from other places have stressed the poorness of reactions in infected tissues, the tendency of infections to spread, the production of necrosis where suppuration would be more usual, and the failure, in general, of infections to respond to therapy. Recent experience at Kampala, where the importance of complications is receding as an understanding of the nature of the disease is growing, suggests that observations of this kind will become fewer as modern methods of dietetic treatment are combined with suitable antibiotics. Deaths from pneumonia have been getting progressively fewer, and fewer children under treatment for kwashiorkor have died of any other infective condition during recent years.

The question of the extent to which infections contribute to the aetiology of kwashiorkor is very difficult to answer. No children in temperate zones, or in the Tropics, pass the first and second years of life without attacks of some minor or major infection, especially of the upper respiratory tract, and the children found to have kwashiorkor are not exceptions to this rule. It is fairly obvious, however, that something in addition to infection is needed to cause kwashiorkor.

If an infection attacks a child with kwashiorkor, it is probable that the picture seen will include signs of the infection as well as those of the kwashiorkor. Thus, to take very obvious examples, with poliomyelitis the legs may become paralysed and with infective hepatitis there may be jaundice—in addition to the stunted growth, the dyspigmentation and the oedema of the kwashiorkor. In other cases the infection may intensify certain of the essential signs of kwashiorkor. For example, malaria causes anaemia even in well-fed infants ; if it complicates kwashiorkor, the anaemia may be severe. The anaemia will be partly nutritional and partly parasitic, and it may be very difficult to determine the exact contributions of the one or the other cause. It may be impossible unless, without changing the diet, the malaria is first treated and the improvement in the blood-count established, and then finally the kwashiorkor is treated. In practice this would be a dangerous procedure.

Can infections cause some or all of the signs of kwashiorkor to appear in well-fed subjects, or will they do so only if the diet has been inadequate in some respect ? These questions cannot be fully answered at the present time and it is proposed to discuss only a few of the many issues involved. It is very doubtful if any infection can produce *all* the signs of kwashiorkor in any child who has been well fed. If the infection reduces the intake of a balanced diet, then the signs of " undernutrition on a balanced diet " are to be expected. The signs appear in the course of tuberculosis and chronic septic disorders in well-fed children in Europe and America. If the infection reduces the intake of a diet which is not well balanced, but has a low protein carbohydrate ratio, the signs of " undernutrition on a protein-poor diet " may appear, producing a clinical picture resembling in some respects that seen in kwashiorkor. In some infectious illnesses—kala-azar and hookworm anaemia are examples—the intake of food cannot be increased until the infection is overcome and appetite improves. When that stage is reached the signs of malnutrition disappear.

Certain infections may make extra demands on protein metabolism, and even if they are not accompanied by high fever, will thus increase still further the inadequacy of a diet already short of protein. The infections may selectively affect organs or functions that are already disturbed. Venkatachalam and Patwardhan (1952–53) have suggested that ascaris infections may play a part in increasing the severity of kwashiorkor by reducing the absorption of nitrogen from the gut ; many other infections, especially those of the respiratory tract, are known to decrease the formation of pancreatic enzymes in normal infants (Véghelyi, 1948b, 1949), and it is possible that their effects might be more severe, or of longer duration, in children suffering from mild or severe kwashiorkor. This may explain the effects noted by Welbourn (1951) of respiratory infections on the growth curves of children known to be taking a diet with a low protein/calorie ratio. If the infections attacked well-fed children, there was a loss of weight, but a period of rapid compensatory growth during convalescence ; if they attacked malnourished children, however, there was a prolonged deflection of the growth curve.

8. Variations in the pattern of kwashiorkor

Very few qualified observers have so far been able to see kwashiorkor in a number of different lands, or arising in many different circumstances. It seems to be the present, and enlightened, policy of some of the international organizations to send one or two of their people to explore widely, and the results should be most profitable. Up to now, work on the disease has been done by individuals, or small groups, whose first-hand experience has usually been limited to a small part of the world. In consequence, there has been a tendency to speak of variations in the pattern of kwashiorkor—a tendency which is easy to understand in view of the lack of basic data. Some of the alleged variations obviously arise fortuitously—for example, when vitamin deficiencies and infections are superimposed ; others seem to merit more discussion, because they may throw light on the understanding of the basic disease.

The degree of severity of the attack is likely to produce wide variations ; some children—usually those with oedema—are seriously ill, and others who appear to have only one or two of the stigmata, such as brownness of the tips of the hair and a slight retardation of growth—are much less ill. (It is in fact uncertain if these children should be regarded as cases of kwashiorkor at all.) It is, however, inherent in the nature of any nutritional disease that all grades of severity may occur. Those who suffer less severely are usually more numerous, and the normal range of physiological variation fades imperceptibly into a state of disease. Some investigators display much irritation with the impossibility of avoiding this fact; they want to collect frank, obvious and marked cases of a nutritional disorder, and become vexed if that is, from the very nature of things, not always practicable.

There are considerable variations in the duration of the disease. Most untreated cases of severe kwashiorkor die, but others who are given what must be inadequate treatment may survive. They may appear to make a slow but complete recovery, or they may eventually become thin and stunted. It is probable that the majority of cases of mild kwashiorkor never develop signs of serious illness, but survive for many months or years, slightly underweight, sometimes with dyspigmented hair, and with only minor changes in serum chemistry and in the structure of the tissues. The stellate fibrosis of the liver found in later life may be due, not to the severity or duration of the fatty changes which accompany an attack of kwashiorkor, but to other changes occurring very slowly as the result of the adolescent and the adult remaining on diets which are low in protein (p. 261).

A third variant is that due to the age of the patient. Kwashiorkor in a child one year old may affect certain tissues which are then developing rapidly. If it occurs at a much later age—for instance in adolescence—the tissues affected may be different. It appears likely that kwashiorkor always disturbs growth, which itself demands much protein during the first few years of life. In a later chapter (p. 249) it will be suggested that in adult life a disease may occur which resembles in many respects kwashiorkor in childhood. If there are differences they may depend on the cessation of growth in stature, and of some forms of development.

Cases have been described in which signs of undernutrition are combined with those of kwashiorkor (Waterlow, 1948a), and it is possible that some cases recently reported from Djakarta, in Indonesia (Sutedgo, 1953, personal communication), are of this kind.

The weaning diet was much-diluted condensed milk. Some of the children who had received no breast milk at all, or very little, were only 4 months old when they were brought to hospital, but children of all ages up to 7 years were seen and most were aged from 1 to 3 years. The history always included diarrhoea, but it was oedema that was the chief feature. Growth had been arrested, and except in the oedematous parts the children were very thin. There were alterations of the hair and skin. The liver was usually considerably enlarged, and was fatty and fibrotic. There was no splenomegaly. Anaemia, with haemoglobin about 7·0 g./100 ml. and a colour index a little less than unity, was a constant finding, but there was no serious hookworm infestation and very little malaria. The children were hungry, and took all the food they were given ; their stools seemed to contain some fat, but not much other undigested food. Serum albumen was reduced, but cholesterol was normal. It is likely that in these children there was an element of starvation added to kwashiorkor.

Altmann (1948) regarded children who may have been somewhat similar as ' atrophic ' cases of kwashiorkor. There have been few recent observations on ' atrophic ' cases, and their status is difficult to decide. At Kampala, they were perhaps more common when kwashiorkor was treated with *small* amounts of whole cow's milk, or when the protein content of the diet was *slightly* improved, as in the times before treatment with high-protein diets was instituted. The treatment might have done no more than produce " undernutrition on a balanced diet " (p. 59). The observations, however, have been too few for certainty, and it should not be assumed that all the " atrophic " cases arise in this manner.

Any case of kwashiorkor, even if uncomplicated, presents many different signs. The signs vary from case to case, and some clinicians have considered that this variability demands the recognition of many varieties of kwashiorkor. Some signs appear always to be present in severe cases : mental apathy, anorexia, failure of growth, wasted muscles, a low serum albumen, decreased formation of pancreatic enzymes, many changes in the serum chemistry (p. 163) and slight anaemia. Others are not always found : oedema, diarrhoea, and a fatty liver. Certain signs, such as the fully-developed dermatosis, are only present in very severe cases. The anaemia, although usually normocytic, may be slightly macrocytic ; some children retain their appetite, and others have black hair. Should these variable signs be regarded as constituting so many new varieties of the disease ? In the present stage of knowledge, it would appear unwise to do so for all the signs change, in the direction of improvement, if the case is treated with a protein-rich diet. Doubtless there is actually a difference between oedematous and non-oedematous cases (to cite but one example), but it is probable that the proportion of interstitial fluid in the body is increased even if no oedema can be seen, so that separation on the grounds of the visibility of the oedema would be artificial. It is very desirable that there should be more investigation of the causes of the oedema and, indeed, of all the other signs. Until the investigation has been done it is premature to speak of different varieties of kwashiorkor, since there is remarkable consistency in the basic pathology and biochemistry of the disease, despite the considerable differences in the signs.

THE CLINICAL PICTURE

Signs in severe cases

1. *History and manner of onset.* It is difficult to obtain precise information concerning the manner of onset, but the very vagueness of most replies suggests that the child has been ailing for some time. Often an unconvincing statement is given that the child has been ill for only a little while, but this usually refers to the duration of the oedema, or a period of gastro-intestinal upset, or the period of serious illness (Delon, 1950c). Those who have watched the slow onset of the disease from child welfare clinics have noted that a long period of retarded growth and diminished vigour, together with some dyspigmentation of the hair, preceded the period of serious and recognizable illness (Williams, 1931–32 ; Welbourn, 1953). Very few have observed the onset of a large epidemic of kwashiorkor as did Véghelyi (1950a). He described three stages in the evolution of the disease ; a stationary or falling body-weight with reduction of the pancreatic enzymes ; the onset of diarrhoea, and increasing signs of hepatic dysfunction ; and the appearance of oedema.

In many children the signs of severe kwashiorkor appear within a few weeks or months of weaning. The breast-fed children showing the signs are usually in their second year, when the breast is presumably secreting very little milk, and acting mainly as a comforter.

2. *Growth and development.* Kwashiorkor seems always to be associated with an arrest of growth, and in a long experience of the disease no exception to this rule has been noticed (H. C. T.). The literature does not appear to include any record of a case in which the weight was normal for the age. It is possible that a false approximation might occur if the oedema was very gross, but the total weight, including the oedema, is usually definitely subnormal, as in a series reported from Kampala in which oedema accounted for 20 to 30 per cent of the gross weight (Trowell, Davies and Dean, 1952). The weights of these children on admission to hospital are shown in Fig. 1*a*, and the weights of children seen in clinics at Djakarta (Indonesia) by Oomen (1953) are shown in Fig. 1*b*.

There are few reliable records of the growth of children who subsequently developed kwashiorkor, but to judge from the original weight curves given by Williams (1931–32) and the records of child welfare clinics (Welbourn, 1951, 1953) there can be little doubt that arrest in growth occurs before the disease is usually recognized. The weight of the children brought to Mulago Hospital, Kampala, at the age of about 18 months is that which was probably reached at 5 or 6 months. There appears to have been some skeletal development since then : there may have been also an increase in weight, but the increase has been lost. Oomen's results (Fig. 1*c*) show that the length of his patients was very often well below the local average.

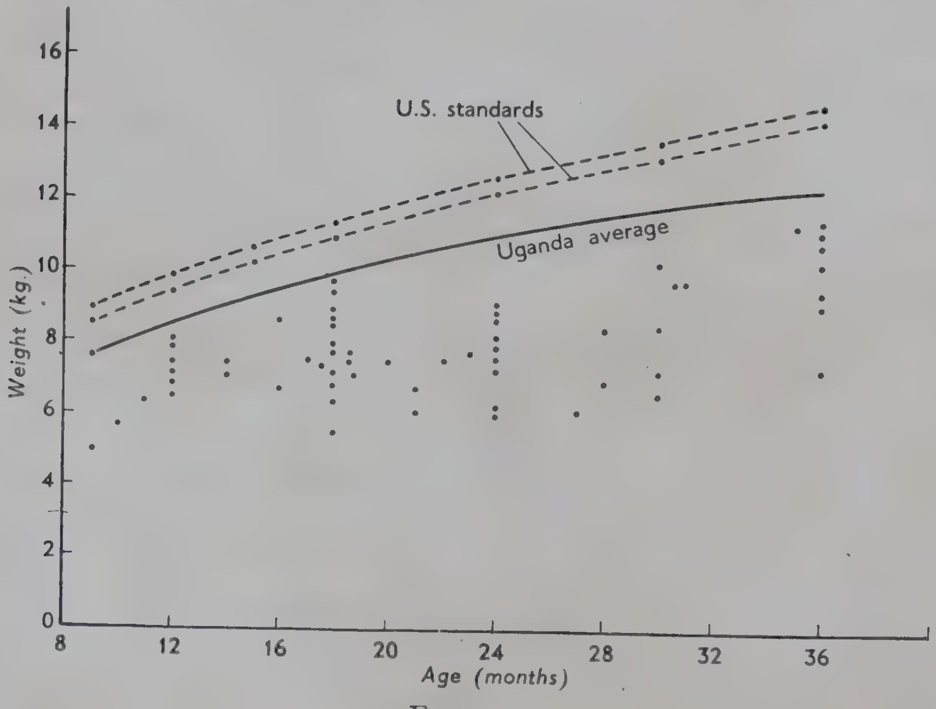


FIG. 1*a*.

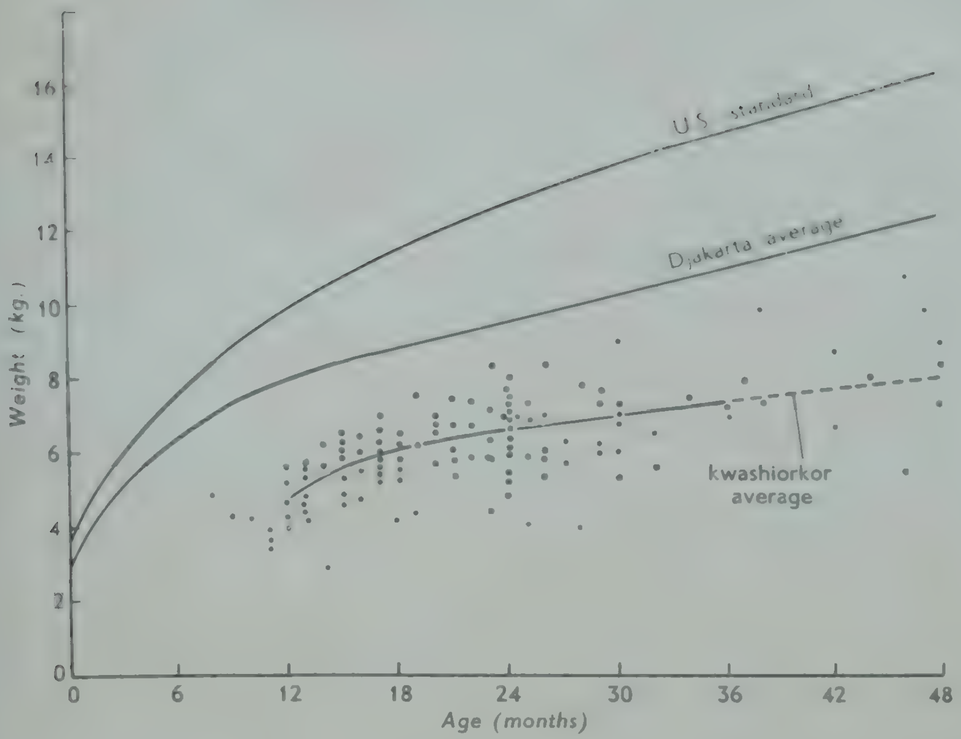


FIG. 1b.

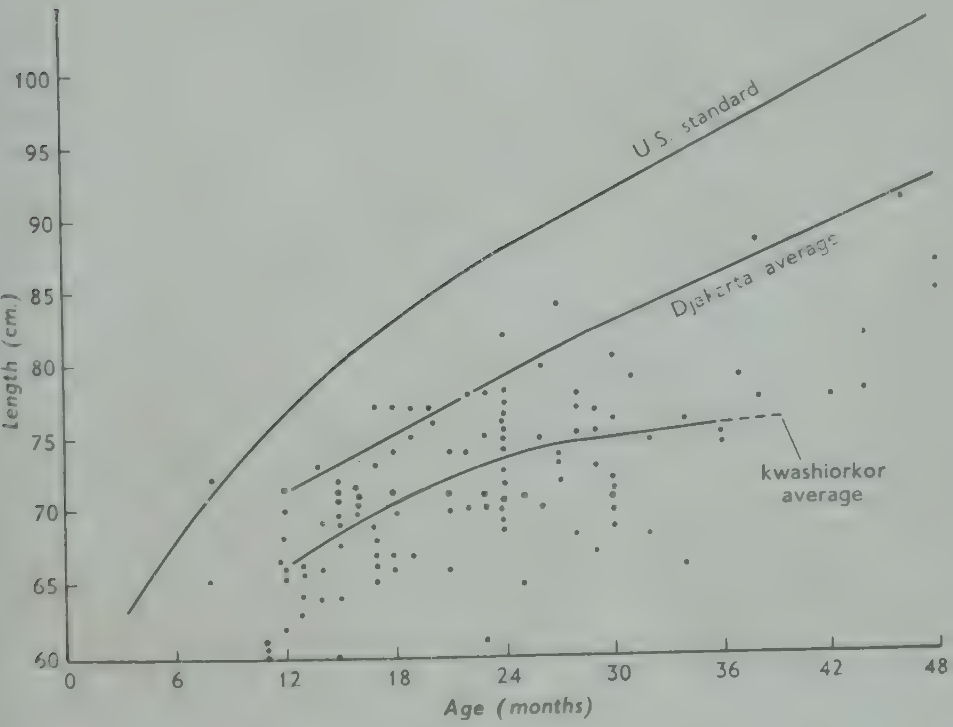


FIG. 1c.

FIG. 1.

(a) Weights of children admitted to Mulago Hospital, Kampala, with the gnosis of kwashiorkor (Trowell, Davies and Dean, 1952).

(b) and (c) Weights and lengths of children seen at Djakarta clinics by Oomen 953).

The U.S. standards referred to are those of Meredith (1935) and Boynton 936).

Usually, the weight of the child seems to be more affected than the length, and Senecal (1953, personal communication) has made the ingenious suggestion that the ratio of length to weight might be used as a diagnostic criterion. The suggestion might not be favourably received, however, by writers of the same opinion as Miranda (1948), who says that " height is a better index of protein nutrition than weight, which is rather an index of caloric deficiency ".

A hint of disproportion in the various parts of the body is often a help in estimating the true age, and therefore the degree of retarded development. Radiological examination of the bones is at the moment of limited value because of the absence of normal standards, and uncertainty concerning the effects of nutrition on growth. The hands of children admitted to Mulago Hospital, Kampala, with the diagnosis of kwashiorkor have been X-rayed in recent years and the results suggested some retardation of bony development, at least by American and European standards. The validity of using such standards is questionable, but at the present time local standards, which would be more suitable, are not available (Dean, 1953c). Gopalan and Gomez, working in Coonoor, South India, and in Mexico City have found evidence of gross retardation (personal communications, 1953). Gopalan has seen children four and five years old whose hands have the bony structure expected in a child less than a year old, a discrepancy so great that causes in addition to kwashiorkor seemed likely. Autret and Behar (1954), although they do not appear to consider that the bony condition in Central American children suffering from the multiple-deficiency syndrome is of great importance, cite the opinion of one Costa Rican doctor (Saénz-Herrera) who thinks that it can be exactly correlated with the dyspigmentation of the hair (p. 80).

Stransky and Dauis-Lawas (1950a) quoted figures for height, and circumference of the head and chest, which were said to show a retardation in growth and Dricot, Beheyt and Charles (1951) thought that some of the children they investigated in late childhood and adolescence were shorter in height than normal. Adequate local standards for healthy children were not, however, quoted for the purpose of comparison. There does not seem to be undue postponement of the closing of the anterior fontanelle. It is not uncommon to see a very undersized child from whom blood cannot be taken by this route.

The transverse lines which are often seen in X-rays of the long bones of Uganda children may well represent an effect of kwashiorkor, as such lines are known to indicate periods of arrested growth. So far, however, it has not been possible to prove this point by X-ray examination during and after an attack. A generalized osteoporosis has been described (Meneghello, Espinosa and Coronel, 1949; Janssen and le Roux, 1950a; Peña Chavarría, 1953, personal communication), but the interpretation of this finding is doubtful because adequate 'controls'—healthy normal children of the same age—were not always to be obtained.

No delay in the eruption of the teeth has been detected in children admitted to hospital in Kampala, and the incongruous sight of a tiny child with its mouth crowded with teeth is not unusual. S. Chaudhuri (1950) thought the dental development of New Delhi children was normal, and it is likely that the teeth which have presumably been laid down and formed during a period of adequate nutrition during intra-uterine life and breast feeding, are usually well formed. There have not been many reports of dental caries, but according to Autret and Behar (1954), they are frequent and severe in cases of the "multiple-deficiency syndrome" in Central America, and K. G. Chaudhuri (1952) found them in one-third of the children he investigated in Calcutta. Hypoplasia of the enamel is seen occasionally, but probably has no connection with kwashiorkor. Gomez (1953, personal communication) has been impressed with the excellent state of the gums in the Mexican children. He says that they often appear to be the only part of the body that is healthy.

The frequency of undescended testicles has been the subject of comment (Hanafy, 1947; Oomen, 1951), but is another matter of doubtful significance.

It is obvious that very little is known with certainty about the effects of kwashiorkor on development. There are probably many subtle effects awaiting discovery.

3. *General appearance. Subcutaneous fat. Muscle.* The general appearance of a case of kwashiorkor is so distinctive that suspicions are often aroused as soon as the child is seen. If the hair nd skin are dyspigmented and there is some generalized oedema, the diagnosis can often be made at first sight. The child may appear to be asleep; he is miserable when aroused, his eyes may be red, his nose discharging and his mouth dribbling. Because he seems to esent both light and cold, he is swaddled in clothes and kept covered s long as possible. When the clothes are unwrapped, he almost

invariably starts to cry as he feels the cold air, or when attempts are made to move his limbs. The cheeks may have looked chubby, but as soon as the whole body can be seen, it is realized that the feet and even the hands are swollen and that the deceptive chubbiness is part of a generalized condition of oedema. The eyes are often puffy, and in advanced cases the oedema may be so severe that it suggests acute nephritis.

If there is much oedema it may be impossible to assess the amount of subcutaneous fat, but if only the feet and hands are swollen, some estimate can be made of the fat in the upper arm and thighs, and over the trunk. In a fair proportion of cases there is a disconcerting amount of subcutaneous fat (Gelfand, 1946; Davies, 1951). In other cases, especially if there has been a long period of anorexia, low food intake and vomiting, coupled with poor digestion of food and intractable diarrhoea, much subcutaneous fat is lost, although this may not be obvious until the covering of oedema has disappeared under the correct dietetic treatment. When the oedematous limbs are handled it may be found that the skin is stone cold, even if the day is not particularly cool. The feet and hands are often dusky purple in colour, as if there was some stasis of blood and dilation of the skin vessels. Pressure causes the skin to blanch, and the blood returns slowly. The pressure may not cause pain but even the lightest touch is usually resented.

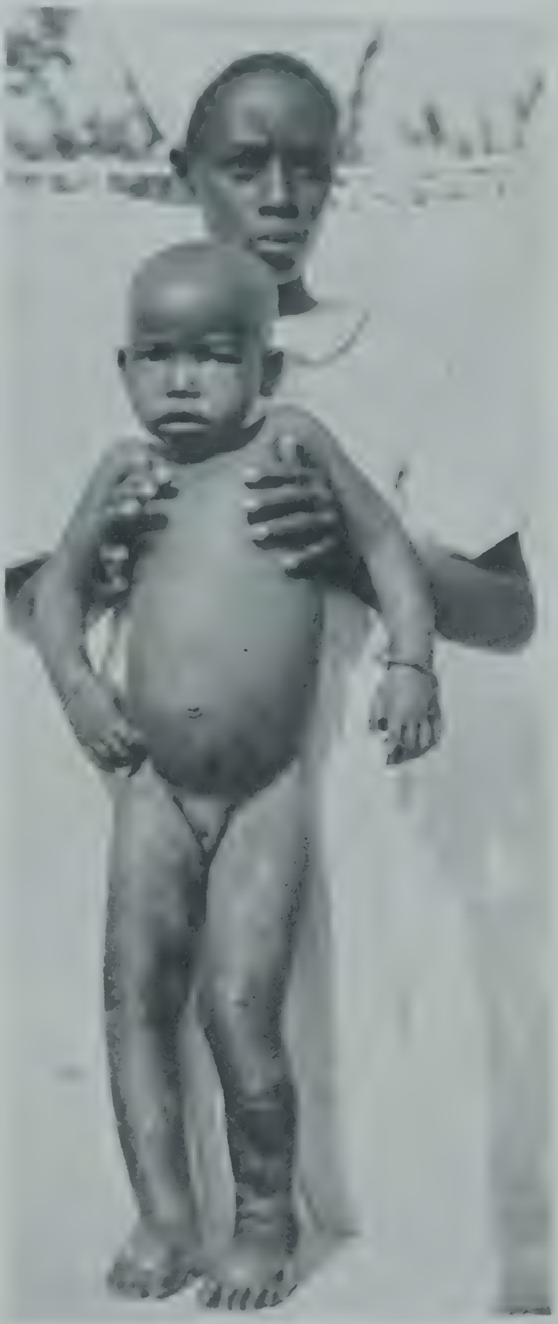
It may be very difficult to reach any definite opinion on the state of the muscles. Children who are severely ill tend to hold their arms and legs tightly in the flexed position, perhaps to minimize the discomfort of the moist and desquamating dermatosis which affects the groins and axillae (p. 87). All movements of the limbs are resisted, but it is difficult to say how far this is due to mental irritability or to pain. The limbs are spontaneously moved very little and the immobility may suggest paralysis, which was actually reported at one time (Castellanos, 1935). It has also been said that in advanced cases the reaction of degeneration may occur in the legs, and that chronaxie is greatly increased although true paralysis is not present (Pagola, 1948). The presence of gross oedema often conceals the wasting in the muscles, but it may be possible to palpate the attenuated muscle bellies in the upper parts of the limbs, where there is less oedema. The gross degree of muscular wasting becomes visible during convalescence when the oedema has disappeared and flabby buttocks and shrunken limbs are revealed (for example, see

Hughes, 1945–46). The loss of muscular tone may then be very striking. It has been said to cause articular changes and to lead to the adoption of attitudes that cause deformities of the sternum and thorax (Flores, 1947) and it may be the cause of the flat-foot and knock-knees frequently seen in children recovering from kwashiorkor.

4. *Oedema*. Many children are brought to hospital because of the oedema, and it is a feature of nearly all cases of advanced kwashiorkor.

So far as can be judged from the parents' statements, the onset of oedema probably marks a transition from the mild to the severe state of the disease in many cases; the transition may occur after what might have been an acute attack of gastro-intestinal trouble, usually shown by diarrhoea, or a period of decreased intake of food such as accompanies many fevers. Oedema has been considered by some workers to indicate that the prognosis is bad, and even hopeless. That is not the view held at Kampala, but it is recognized to be an indication of the need for immediate and adequate treatment.

The oedema appears first on the lower parts of the legs and the dorsum of the foot (Fig. 2). At Kampala the oedema usually pits readily,



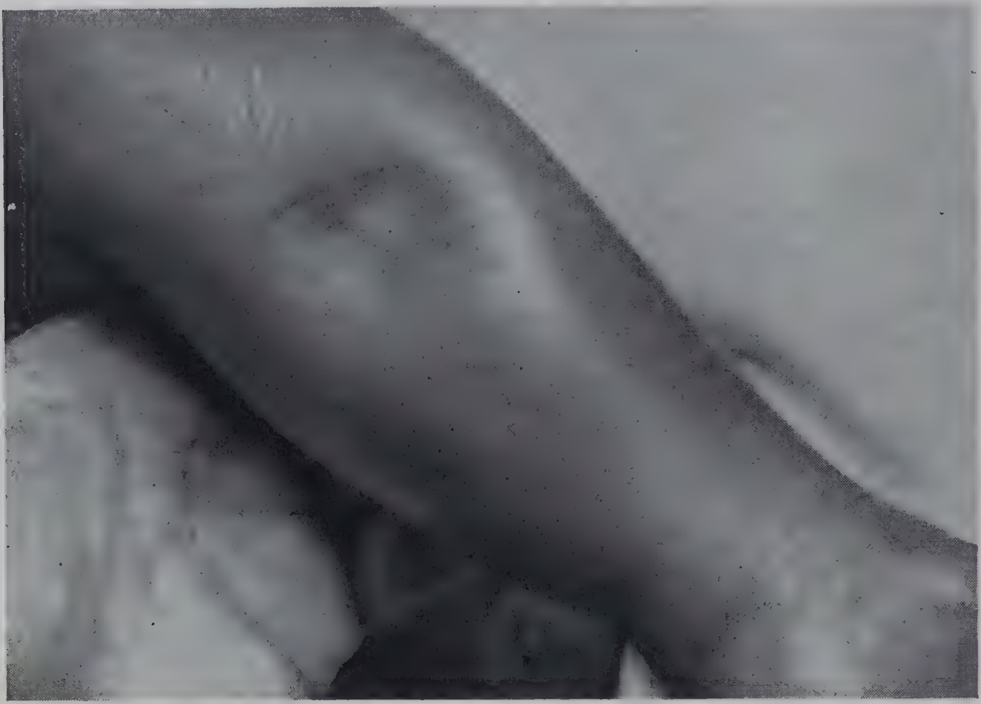
(*a*)

Fig. 2.—Oedema in kwashiorkor.

(*a*) Generalized oedema, showing chiefly in face, hands, legs and feet. A fatal case seen at Kilifi, in the coastal district north of Mombasa (Kenya), by Dr. W. L. Barton. The edge of the liver was said to reach the umbilicus. Note the dermatosis, especially on the lower legs.

(Photograph by Mr. R. Watkins Pitchford.)

and to an observer with experience of hunger oedema in adults there is a notable difference from that condition : the pressure of the thumb or finger seldom appears to cause pain. Oedema which was seen by one of us (R. F. A. D.) in children at Kerugoya, in the neighbourhood of Fort Hall, Kenya, did not pit so readily, and it was less easy to be sure that the pressure was painless. The next site to be involved is the face. The eyes are puffy, especially the lower lids, and the cheeks may seem to droop with the heaviness of the extra fluid they contain (Fig. 3). It has been suggested by Gopalan (1953, personal communication) that the swelling of the cheeks may not be due to oedema : one theory is that it is caused by the persistence of the " sucking pad ", which in infants does not disappear even in severe wasting diseases. Gomez (1953, personal communication) has made sialograms which seem to indicate an anterior prolongation of the parotid. Whatever the cause, the swelling is an interesting and characteristic feature, which has not only been noticed many times in the Tropics, but has also been described as present in children affected by *Mehlnährschaden* (Glanzmann, 1947 ; and see also the illustration given by Rominger, 1931).



(*b*)

Fig. 2.—Oedema in kwashiorkor.

(*b*) Pitting oedema of leg in child admitted to Mulago Hospital.

In African children, the distribution of oedema is much less regular than it is in European children who are suffering from an oedematous condition such as nephritis, and it is sometimes notable in kwashiorkor that the facial oedema is excessive compared with the amount elsewhere. When that happens, the eyes may be almost closed and the apposed surfaces of the lids may begin to lose their skin. The hands, the legs up to the knees, and the arms, are next affected, but the sacrum is only seldom involved, and then very slightly. In many cases the oedema does not seem to have a strong preference for dependent parts, but in others it is noticeable that one cheek or one leg is more swollen than the other, and the explanation is that the child has lain on this side during the preceding night. Although a very severe generalized anasarca has been described by some writers, it is seldom seen to a severe degree in Kampala, unless hookworm anaemia is also present. Oedema of the penis and prepuce may be severe, especially as part of the anasarca, and before the condition was understood circumcision was sometimes undertaken to relieve paraphimosis (Gillman and Gillman, 1951). At Kampala it has not been possible to detect ascites or a pleural effusion in any case uncomplicated by an infection such as tuberculosis, and this has also been the experience of Janssen and le Roux (1950a). Effusions into joints are also unknown.

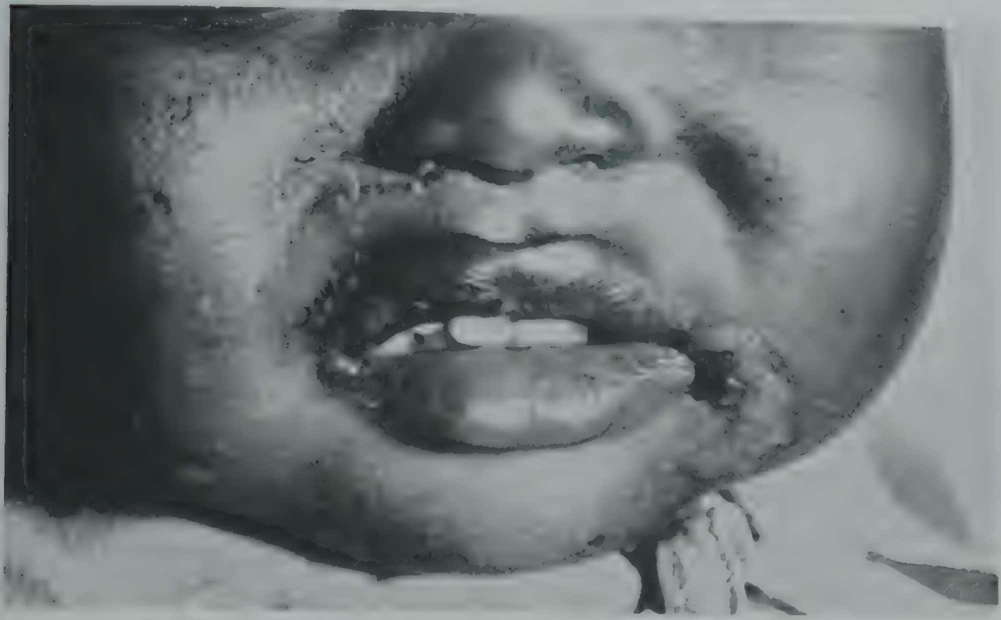


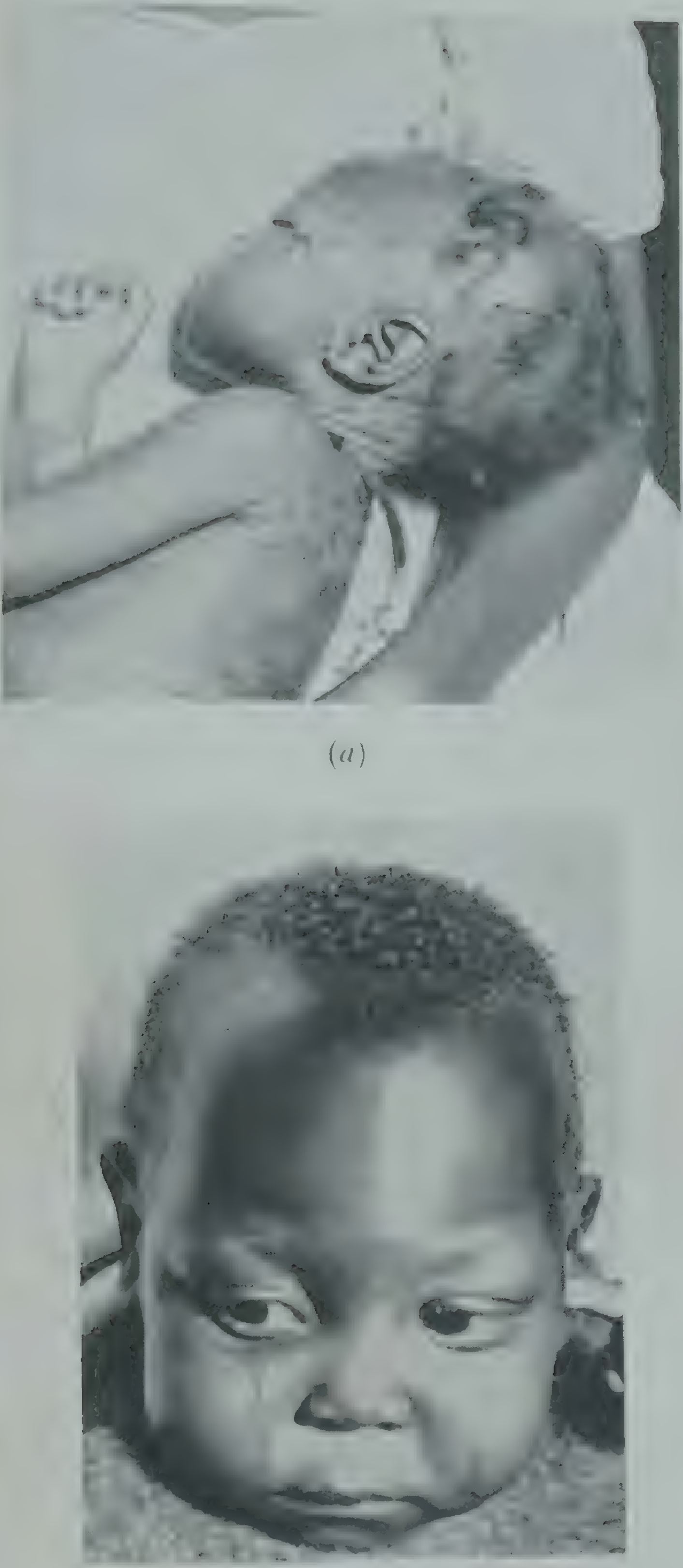
FIG. 3.—Oedema of the face in kwashiorkor. The distortion of the profile of the cheek is characteristic.

It is convenient to mention here a finding which is almost certainly related to the superficial and subcutaneous oedema. If the chest is carefully X-rayed, using a short exposure which permits sharp definition of the lung fields, an area of soft shadow is often found extending outwards in the shape of a wedge with its apex in the hilar region, but with no visible glandular enlargement. There may be more than one such area to be seen in a chest film. The shadows, which were noticed by Flores (1947) and by Gomez (1953, personal communication), can easily be mistaken for those of pneumonic processes, especially as a few moist sounds can sometimes be heard on stethoscope examination. Post-mortem examination, and repeated X-rays, have led to the conclusion at Kampala that the shadows probably represent small collections of fluid. Although this is the most plausible explanation, it must be admitted that it seems strange that the condition never goes to effusion. Presumably the fluid remains in the interstitial spaces. The fluid may be the cause of the slight, unproductive cough which so many of the children have when admitted to hospital. The discharging nose and the slight catarrh of the pharynx may contribute to the cough in some cases.

It is said that whilst oedema is present the urinary volume tends to be low (Dricot, Beheyt and Charles, 1951). Exact measurement is usually very difficult, but there is no doubt that the oedema is lost by diuresis. Once lost, the oedema should not recur. Reports of recurrence, and statements to the effect that recurrence is a bad prognostic sign probably indicate an insufficiency in the diet used for treatment, or the injudicious addition of an ingredient such as salt.

In some places, the incidence of oedema varies from season to season, presumably with changes in food supply. Gomez (1953, personal communication), who receives many cases with or without oedema, thinks that in the oedematous children there has probably been more diarrhoea. The diarrhoea has a seasonal incidence, and so, therefore, has the oedema.

A child showing some of the signs of kwashiorkor, but having no oedema, is not usually seriously ill, but from time to time a severe case is seen without oedema. Cases of this kind appear to be common in certain countries, but uncommon in others. Altmann (1948) in Johannesburg described some of them which he termed ‘ atrophic ’, and found successful treatment very difficult ; out of eight, five died. When a child in the ‘ atrophic ’ state is brought to hospital, it is usually impossible to find out if there has



(*a*)

(*b*)

FIG. 4.—Changes in the hair in kwashiorkor.

(*a*) Sparse hair of altered texture in a severe case, with much skin change
(*b*) Hair altered in colour and texture at the sides of the head, but retaining
me of the healthy curliness at the top of the head. This photograph also shows
e recession of hair from the temporal regions. A mild case.

previously been an oedematous episode, but Gelfand (1946) thought that in some of his cases oedema had never been present. Children under treatment at Kampala have been observed whilst they passed from the oedematous to the ‘ atrophic ’ state, and this seems to be the most likely sequence of events. ‘ Atrophic ’ cases have become rare since improved methods of treatment have been introduced.

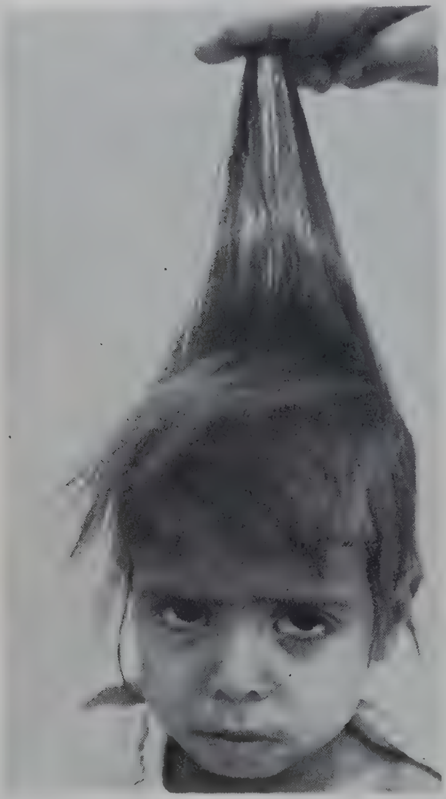


FIG. 5.—The “ flag sign ” in a Costa Rican child 4 years old.

Ten months before the photograph was taken the child was admitted to hospital for treatment of malnutrition. The hair grown during the period of malnutrition is shown half-way along the strand that is being held up : its colour is very pale.

(Photograph supplied by Dr. Peña Chavarría.)

5. *Changes in the hair.* The hair of pure-blooded Africans at birth is black, soft and wavy, but within a few months becomes stiff and curly. Provided the health is good, the hair remains jet black until in middle age some grey appears. In kwashiorkor the African hair takes on many different shades ranging from brownish-black and brown to a pale greyish-brown or even a straw colour (Fig. 4). Completely white hair has never been recorded, and the term ‘ dyspigmentation ’ suggested by Brock and Autret (1952) therefore seems more suitable than the term ‘ achromotrichia ’ used by other authors. It should be borne in mind when considering reports of hair changes that most African tribes use a term meaning ‘ red ’ to cover a large variety of colours —red, brown, chocolate and orange.

Brown hair is present in almost all cases of the disease seen in Kampala. In a few cases, which are typical in every other respect, there appears to be almost no change in the actual colour of the hair but there is always a tendency for it to be softer and straighter than normal. A change in the texture of the hair is therefore a more constant feature than any change in colour. In certain parts of Kenya, notably among the Kikuyu and allied tribes, the hair at times may be grey, straw-coloured, and almost white. This was noted by Stott (1948) and has also been seen by two of the present authors (H. C. T. and R. F. A. D.). The use of some objective standard of measurement would be an advantage but attempts to provide one have failed, partly because exact matching of the various shades is difficult, and partly because the colour changes along the individual hairs, being lighter at the ends. The reason may be that the hair which grows during an episode of kwashiorkor, and perhaps in other states of malnutrition, bleaches more easily than normal hair under the influence of sunlight, ultra-violet light and oxidizing agents, so that the colour change is always maximal towards the tips of the hair, which are the most exposed parts (Platt, 1952 *Proc.*). In some Central American countries the hair changes seem to be very frequent, and the term " rabbit fur " is sometimes used to describe the sparse, straight, pale hair that accompanies the " multiple-deficiency syndrome " (Autret and Behar, 1954).

It is unwise to diagnose kwashiorkor simply upon finding dyspigmentation of the hair ; the other clinical signs, and the response of the hair to protein-rich diets must also be considered. According to Peña Chavarría (1953, personal communication) it is commonly found in Central America that the hair grown during a period of bad nutrition lacks its usual colour, so that alternating bands of dark and pale hair can be seen along a single strand, recording alternating periods of good and bad nutrition. A dozen bands have been counted in a strand 3 to 4 inches long. The " flag sign " (*signe de la bandera*) is illustrated in Fig. 5. The frequency of the sign in Costa Rica is thought to be due to racial factors : the population is largely of Spanish descent, and the normal hair is therefore chestnut brown, a colour that may be particularly susceptible to change. Autret and Behar (1954) say that one Costa Rican doctor estimates the growth of the hair in a child in good health at 12 mm. each month, and in an ill child at 8 mm., and so reads the history of the child in its hair. The sign confirms, incidentally, the Kampala impression that hair once affected never again becomes normal. When treatment is successful, new dark hair grows from the roots (Fig. 24, p. 205).

Hughes (1945–46, 1952) and Oomen (1953) say that large amounts of hair can be removed by a slight pull. The removal often seems to be painless, not being noticed by the child. The hair is certainly lost without trauma, and Fig. 4(*b*) shows the recession of the hair from the temporal regions which is often seen at Kampala. The back of the head, which presumably receives most rubbing when the child lies down, may show some loss of hair. The recession and loss of hair may be extreme.

The dyspigmentation and the change of texture usually occur together. The short hairs at the borders of the scalp, in the temporal regions and over the ears, are affected first, and later the central mass of the hair. In fully developed kwashiorkor, of apparently long duration, not only the tips of the hair but also the roots are altered, so that even if the hair has not been recently cut, it may be impossible to find any new hair of normal appearance. The fine downy body hairs of the trunk and limbs also become pale in colour. The coarser hair of the eyebrows and eyelashes are more resistant, but eventually succumb. The eyebrows may be thinned, and, very occasionally, the eyelashes may be shed.

There does not seem to be a very close correlation between the alteration of the hair and the severity of the general condition. It has been noticed at Kampala that some of the children who are not very ill, but who may have been unwell for a long time, show the greatest alterations. Some of the children most seriously ill, possibly those whose illness has been comparatively short, and who have not been much in the sun, show only a little dyspigmentation, or may have completely black hair (Gelfand, 1946).

Kwashiorkor has been described almost entirely as occurring amongst peoples who have dark hair, and most of these peoples have dark skins as well. Alterations of hair colour are obviously most easily appreciated if the hair normally is jet black and if it can be examined against a dark skin background, and it may be, therefore, that Véghelyi's (1950a) statement that there were no changes in the hair of his Budapest children was not entirely correct; slight changes are very difficult to see. Other explanations are possible. The degree to which the hair is affected undoubtedly varies from one country to another, or from one district to another, and the conditions at Budapest may not have favoured severe changes. There may have been something in the nutritional state of the children or their mothers, before they were subjected to the hardships of the siege, which prevented the changes; the period of acute hardship may have been too short, or there may have been little exposure to sunlight. Dyspigmentation of the hair was not, it seems, a constant feature of the cases of "fatty liver disease" investigated by Waterlow (1948a) in the West Indies, or of those described by Achar and Benjamin (1953) in Madras, or Jayasekera *et al.* (1951) in Ceylon.

It should also be remembered that black negroid hair becomes dull and soft, and may show very slight changes of pigmentation, in any state of undernutrition. Comparable changes do not seem to have been reported in coeliac disease, and no reference to them has been found in the descriptions of prolonged gastro-intestinal illness by the older German paediatricians. It has, however, recently been observed at Marseilles, where many cases of sprue have been collected, that alterations in the texture of the hair can sometimes be seen in that disease (Autret, 1953, personal communication). Undernutrition and starvation, and some wasting diseases such as pituitary cachexia (Simmond's disease), are known to cause changes in the hair, particularly by thinning and loss (Peña Chavarría, Goldman, Saénz-Herrera and Cordero-Carvajal, 1946; Keys, Brožek, Henschel, Mickelson and Taylor, 1950).

6. *Changes in the skin.* The skin in kwashiorkor shows a dyspigmentation comparable to that of the hair, but perhaps occurring somewhat later. The change is obvious only in those whose skin is dark in colour. Circumoral pallor, which can be detected most easily if the cheek is compared with the back of the hand, is the first change, but in advanced cases among negro children the whole of the skin assumes a bronze or reddish hue. It may become coffee-coloured. The brown colour is seen most clearly in the legs where the skin is stretched with oedema, and may there be due as much to the thinning and distension of the skin as to an actual loss of pigment. In addition to this generalized change in pigmentation, there may be more localized losses of pigment, in small punctate areas or in lines. The losses may follow any abrasion, wound or ulceration, or may originate in a scabietic pustule, or scabs and scratches.

In many countries advanced cases of kwashiorkor frequently develop a dermatosis which has probably not been described in any other disease. It is stated that in white-skinned infants the first hange is an erythema (Castellanos, 1935). At first this blanches on pressure, but it is rapidly succeeded within a few hours by mall, dusky-purple patches, which do not blanch. In Kampala, nd in other places where the children have dark skins, small reas of purple staining have often been seen (Fig. 6). They ave a characteristic evolution in untreated cases. In a few hours

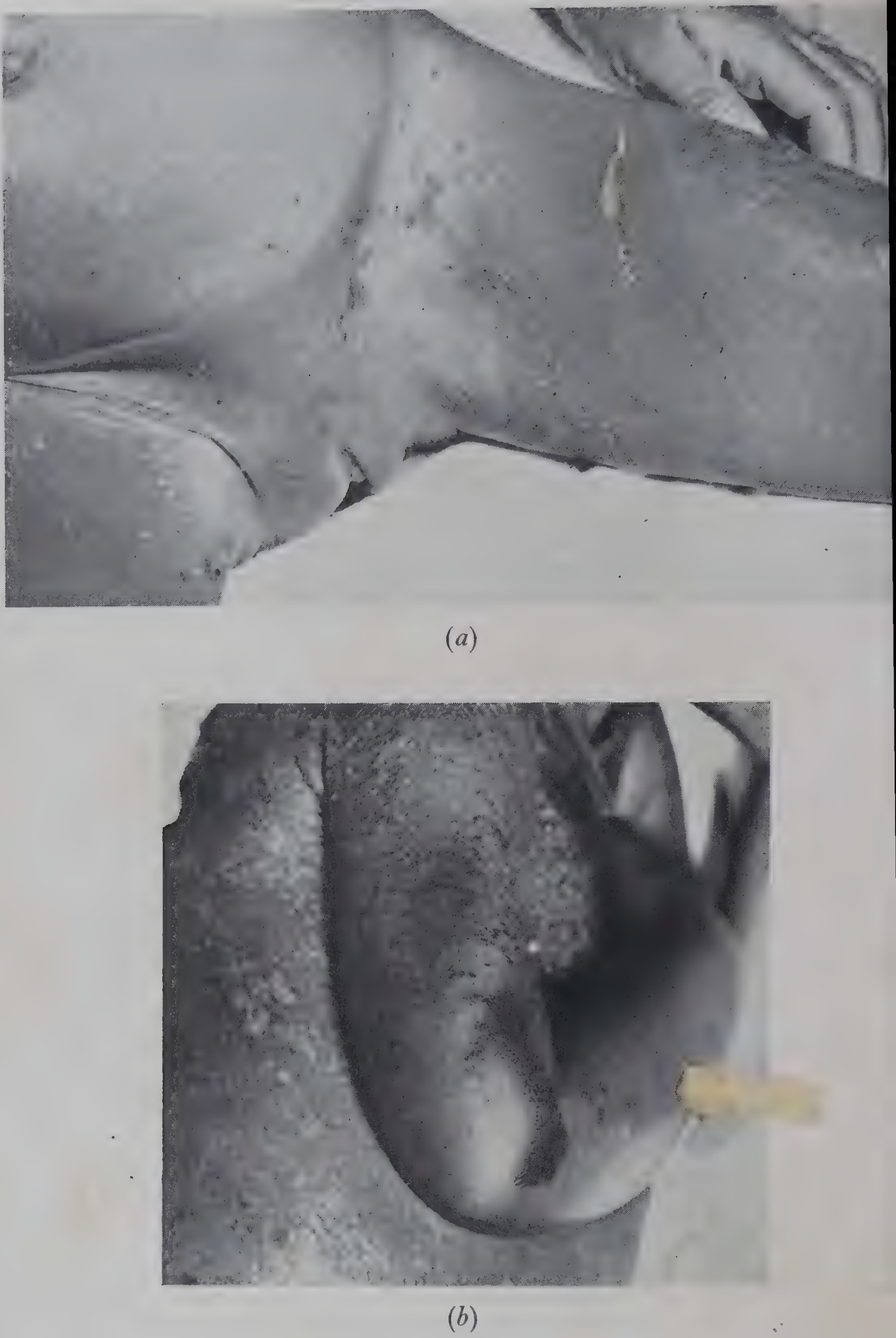


Fig. 6.—Changes in the skin in acute kwashiorkor.

(*a*) Purple patches in inguinal region, at the edges of an area from which skin has already been lost previously.
(*b*) Purple patch over oedema on elbow.

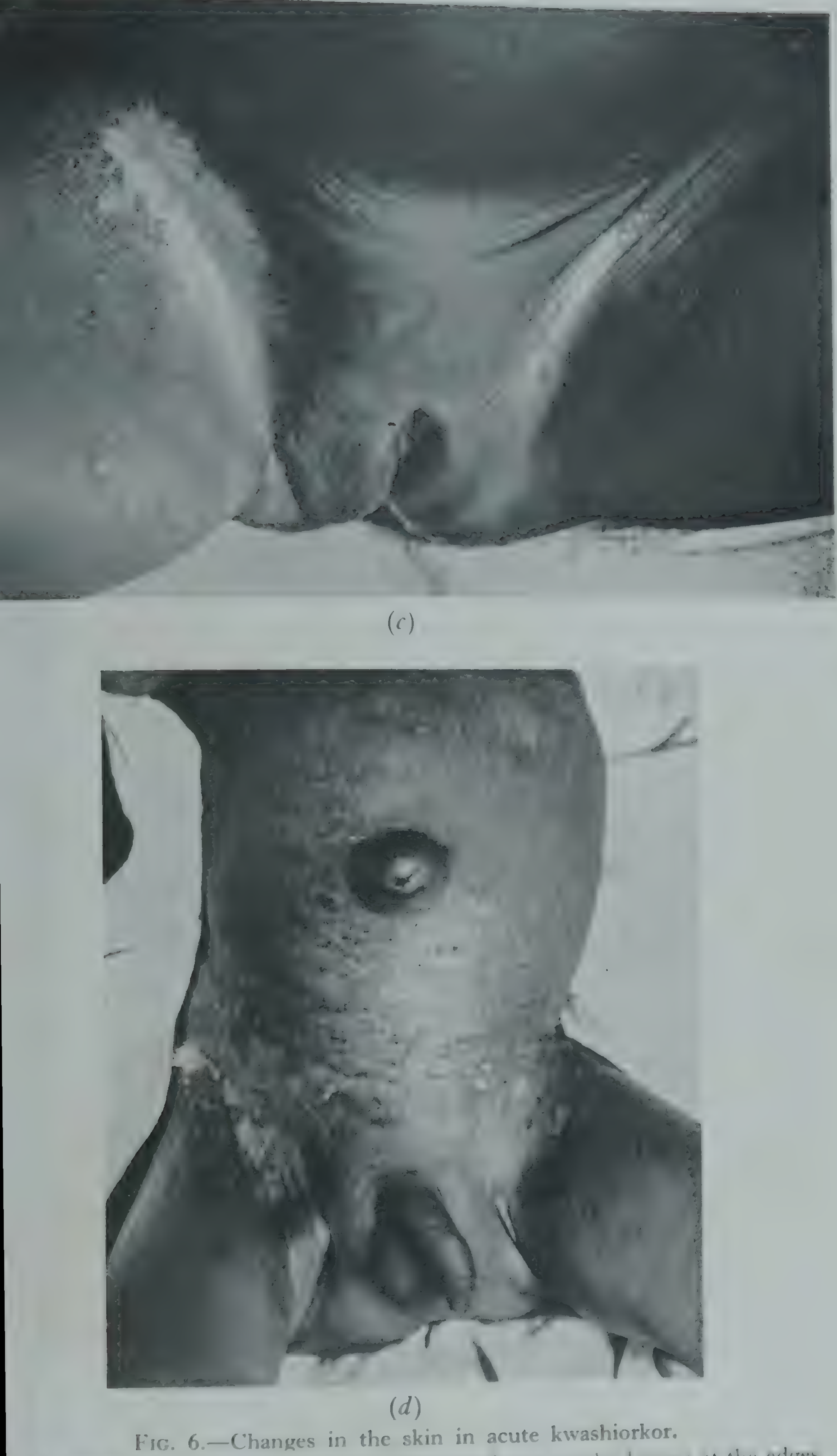
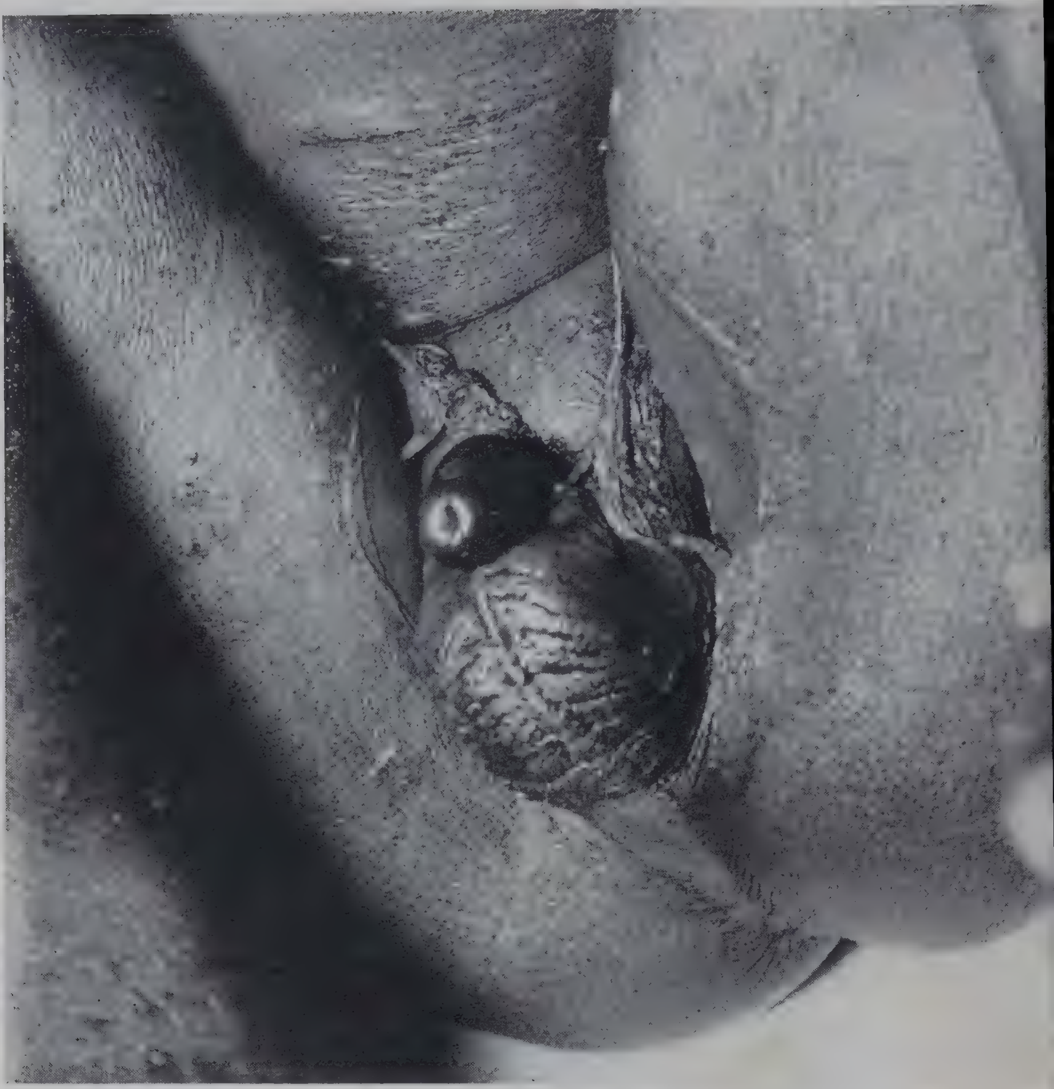


Fig. 6.—Changes in the skin in acute kwashiorkor.

(c) Loss of skin in inguinal regions, with confluent patchy lesions at the edges the unpigmented areas.

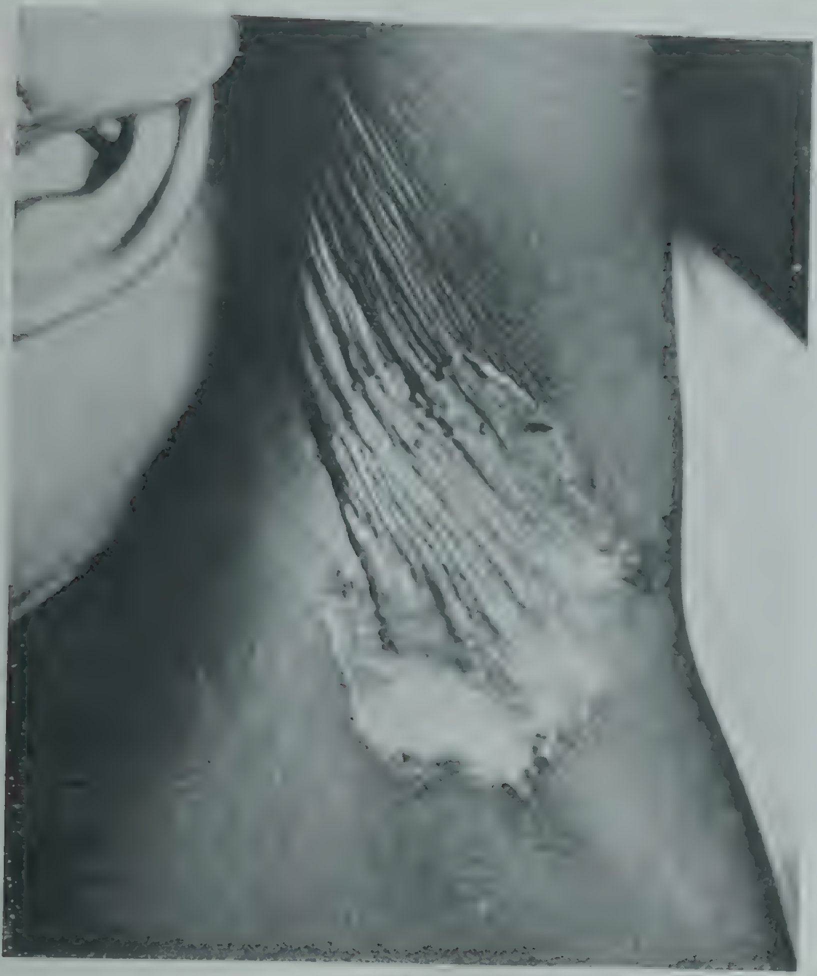
(d) A case in which desquamation is occurring most rapidly in the uppei guinal and waist regions.



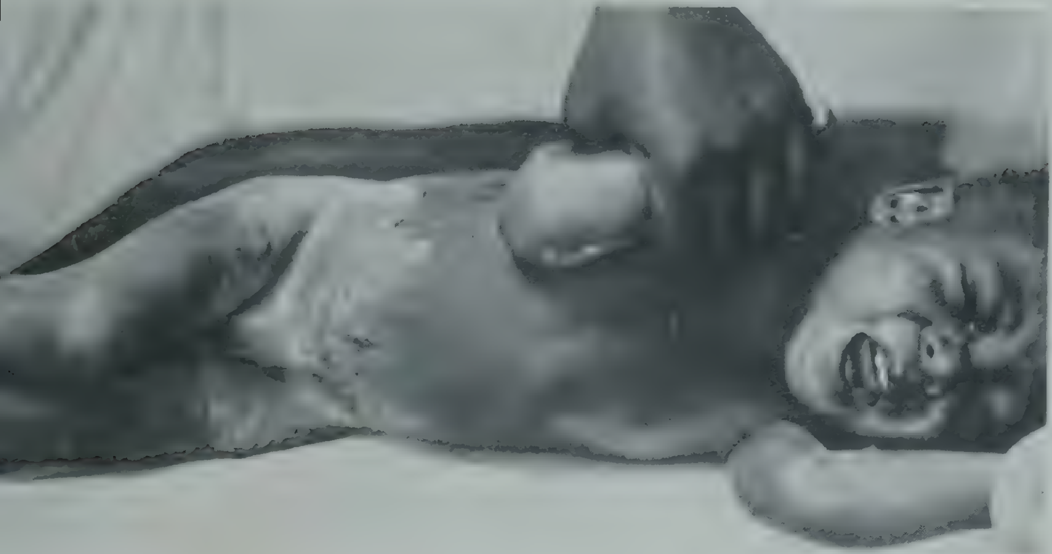
(*e*)

FIG. 6.—Changes in the skin in acute kwashiorkor.

(*e*) Large areas being rapidly denuded of skin in the inguinal regions. Th denuded parts will pour fluid. The skin at the edges of the areas is alread altered, and will soon be lost. The penis is oedematous.



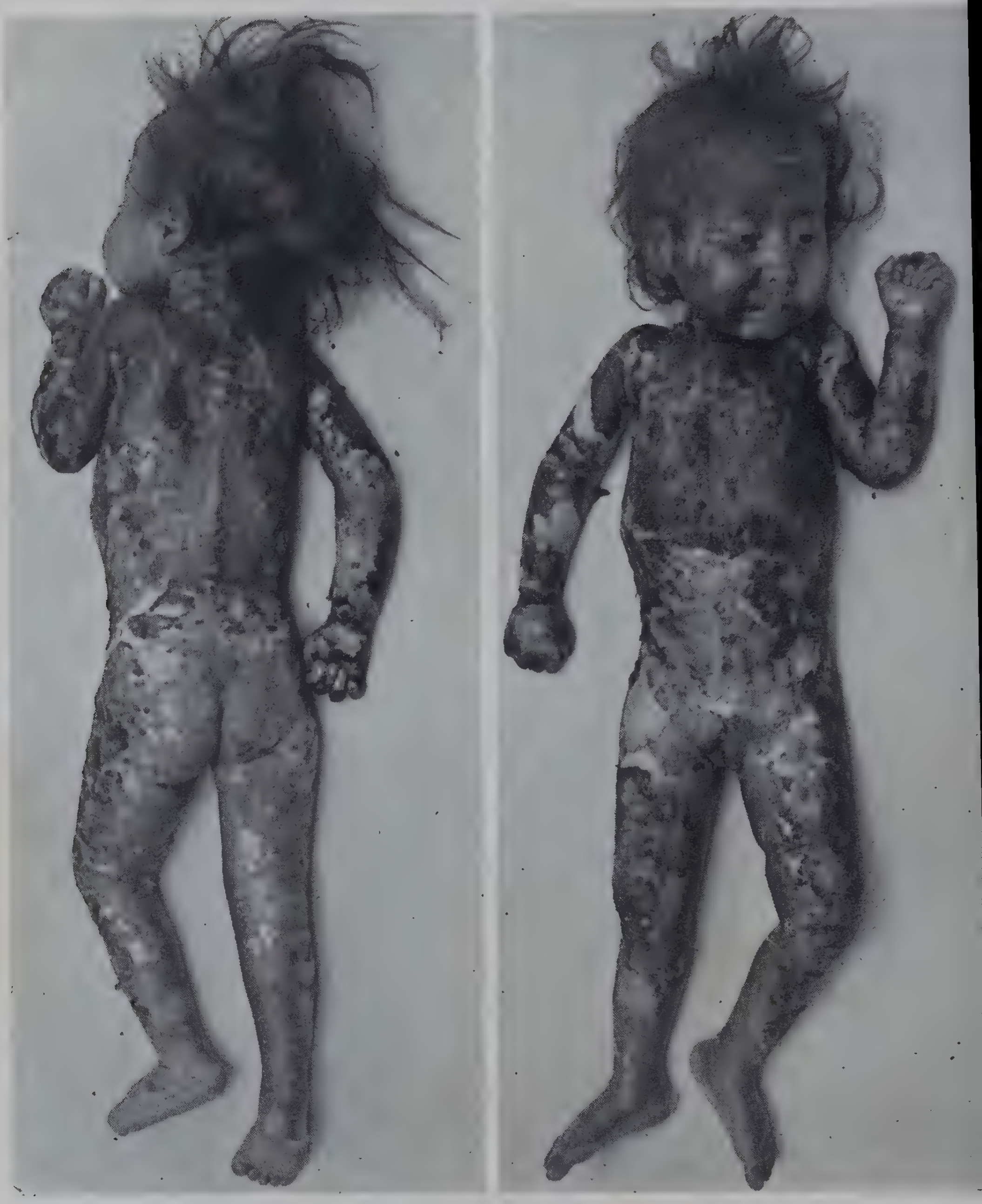
(*f*)



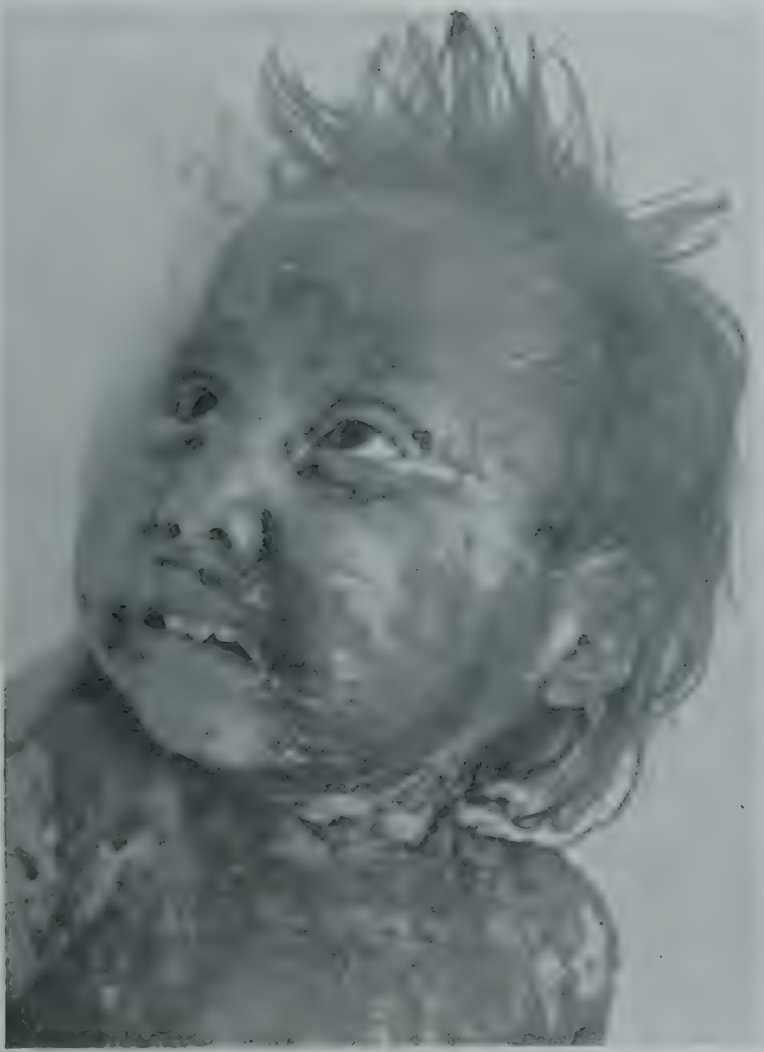
(*g*)

FIG. 6.—Changes in the skin in acute kwashiorkor.

(*f*) A small area of desquamation in the axillary region.
(*g*) General view of skin lesions.



(*h*) (*i*)



(*j*)

FIG. 6.—Changes in the skin in acute kwashiorkor.

(*h*) General view showing desquamation.

(*i*) General view of the same child showing desquamation furthest advanced inguinal regions.

(*j*) Face of the same child as (*h*) and (*i*).

A fatal case seen by Dr. Moïse Behar in Guatemala City.

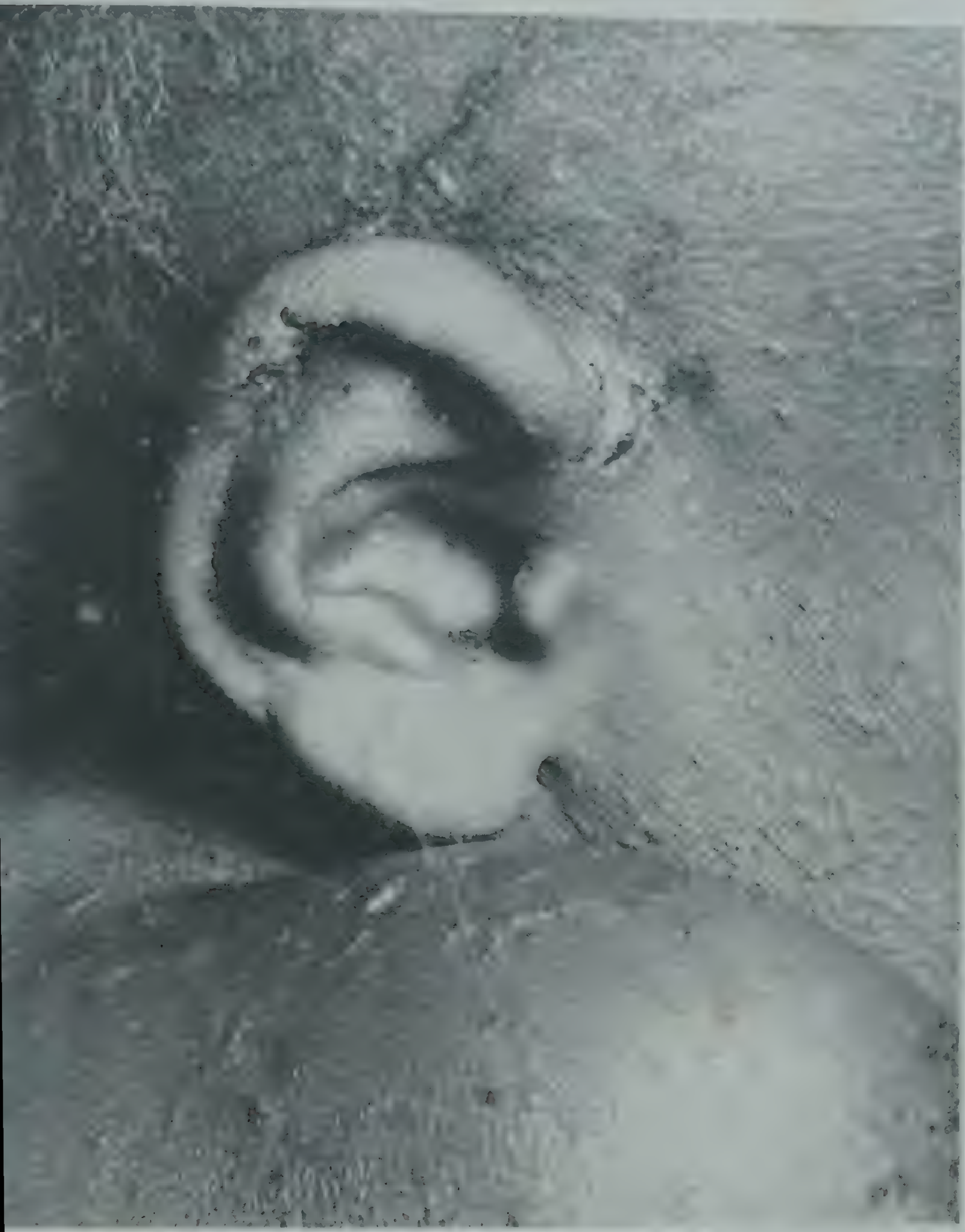
For comparison with Figs. 6 (*a*) to 6 (*g*), which are of children seen in Kampala. the Guatemalan child, the lesions are more extensive, and encroach on the face, d desquamation is extreme.

otographs by the Institute of Nutrition of Central America and Panama, kindly supplied by Dr. Nevin Scrimshaw.)

the purple areas darken; they have a burnished surface and feel almost waxy to the touch. They become almost jet-black in Africans, and brown or coffee-coloured in other races. They have an absolutely sharp edge and appear raised above the surrounding skin, as if small patches of enamel paint had been put on. They are first noticed in those areas subjected to pressure, especially if the pressure is almost continuous and is combined with moistening with sweat or any other secretions or discharge. In Kampala the inguinal region and napkin areas are affected early (Fig. 6 (*c*), (*e*)) but plaques of " enamel paint " may be seen over the trochanters, knees, ankles, elbows, and areas of pressure on the trunk (Fig. 6 (*b*)). The dermatosis seldom appears on areas exposed to sunlight; it usually avoids the feet, back of the hands, and face, and thus differs in distribution from the photosensitive pellagrous eruption. In Central America, however, the face is frequently affected. While new spots of enamel paint are still appearing at the edge of any area of the dermatosis, the central plaques enlarge, coalesce, and start to peel in small or large flakes; in the most acute cases fluid collects below the outer layers of skin, and there may then be some resemblance to a burn (Fig. 6 (*e*)). Whereas mild cases suffer only a little superficial desquamation, the most severe cases have large areas of erosion, in which much of the skin is carried away. Large pale areas of ulceration, having little or no pigment, are disclosed, and at the edge fresh hyperpigmented plaques appear. In untreated cases the affected areas continue to enlarge. The attitudes of flexion usually assumed by the very ill children probably increase the desquamation.

The dermatosis only occurs in severe cases as a terminal event, and this fact should be borne in mind when its absence or rarity in certain reports is being considered. " Enamel-paint dermatosis " seems to be an appropriate name, although the term " crazy pavement dermatosis " (Williams, 1933) cannot be discarded without regret. The term seems, however, to have been applied to skin conditions which have also been called " crackled skin " or " mosaic skin " (Young and Clark, 1939–40) as well as to the true " enamel-paint dermatosis ". The dermatosis is probably peculiar to kwashiorkor and has been described in no other disease. The erosions it forms seldom become severely septic; in oedematous cases they may ooze much fluid, but appear to cause little pain.

In the advanced cases of kwashiorkor which develop the " enamelaint dermatosis ", another condition may occur occasionally in the atural creases in the skin. Linear fissures, " flexural fissures ", they may be called, extending into the subcutaneous tissues, may

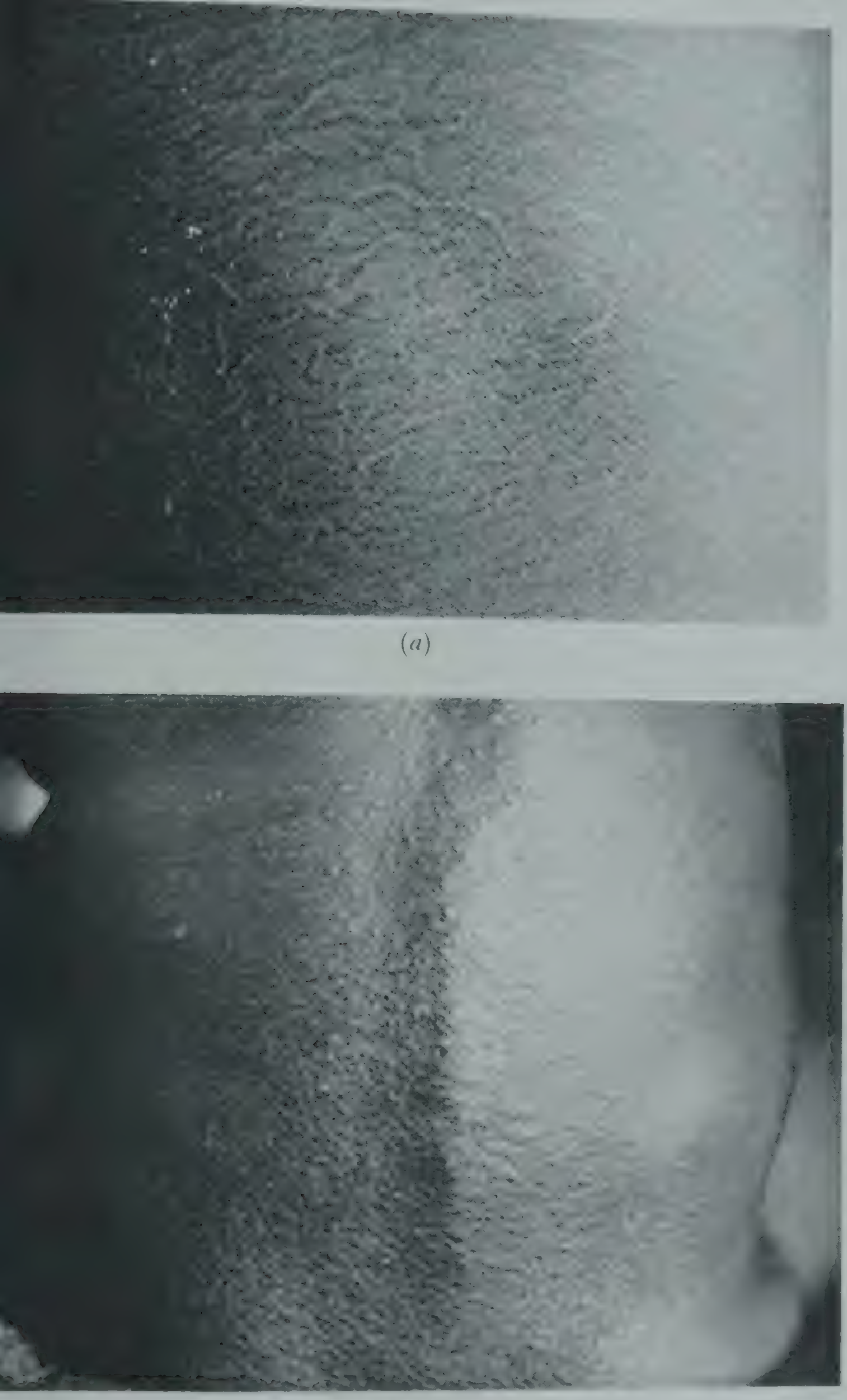


IG. 7.—Fissuring at the junction of the ear and cheek, and on the pinna. Deep fissures often occur behind the ear. A fissure at the corner of the mouth can be seen in Fig. 3.

seen around the pinna of the ear (Fig. 7), at the back of the knee, front of the elbow, in the axilla, between the toes, at the edge of foreskin, and in the centre of the lips. The " flexural fissures " d the enamel-paint dermatosis seem to be produced by the same mechanisms of pressure and movement. Intermittent tension appears to be able to cause similar fissures to appear at the corners of the mouth. These fissures are crusted and bleed easily; they do not have the heaped-up, sodden appearance of the angular stomatitis of riboflavin deficiency. The lesions show signs of healing within a few days of the starting of a high protein diet, but in untreated cases they progress until death occurs.

None of the manifestations of the "enamel-paint dermatosis" were described in *Mehlnährschaden* in Germany, and it did not apparently accompany the "nutritional oedema" of infants in Budapest (Véghelyi, 1950a); the dermatosis was, however, noted by Petrides (1948) in Greece. It occurs in Dakar (Fig. 20, p. 189) and Senecal (1953, personal communication) considers that the condition he sees there is very similar to that he has seen in Haïti and Cuba. One of the present writers (R. F. A. D.) can vouch for the similarity of the lesions seen in Kampala to those common in Guatemala; in Central America, however, it seems that the face is affected more often than it is in Kampala, and desquamation is even more extensive. (Fig. 6 (*h*), (*i*), (*j*).)

One of the milder skin signs of kwashiorkor is a kind of dryness, with an increase in the deeper skin lines that goes on to a very fine desquamation. There are large burnished areas of epidermis which may only crack along the natural lines, and little actual desquamation may be visible to the naked eye; it is a condition often referred to as "mosaic skin" (Fig. 8 (*a*)). If the process becomes more severe, areas of "crackled skin" (Platt, 1945) may be produced. The precise aetiology of these conditions is uncertain and it is probable that they are non-specific signs which may appear in any state of undernutrition (McKenzie, 1941–42; McCance and Barrett, 1951). Be that as it may, they are common in kwashiorkor in children, but usually remain slight, especially in infants. They are more common, and more severe, in states of protein malnutrition in adults (Nicholls, 1940–41, and see p. 256) in whom thick flaky desquamation may occur soon after a high-protein diet is started. In adults, there may also occur large areas of hyperpigmented skin—"reptile skin" or "elephant skin". This is never seen in kwashiorkor in children. The most common sites for the appearance of "mosaic", "crackled" or "elephant" skin are the shins, the outer side of the thighs and the back of the trunk, but other parts of the limbs and even the face may be affected.



(a)

(b)

FIG. 8.—Changes in the skin in kwashiorkor.

(a) "Mosaic" skin on the back, which may end in slight branny desquamation.
(b) "Mosaic" or "crackled" skin, advancing to a more severe form of rmatosis in which there will probably be desquamation.

If glazed and slightly hyperpigmented areas of " mosaic skin " or " crackled skin " occur over parts, especially the lower legs, that are distended with oedema, the appearances may be very distinctive. The stretching causes lines, almost white in colour, that mark off irregularly-shaped areas (Trowell, 1937, and see Fig. 9). There is

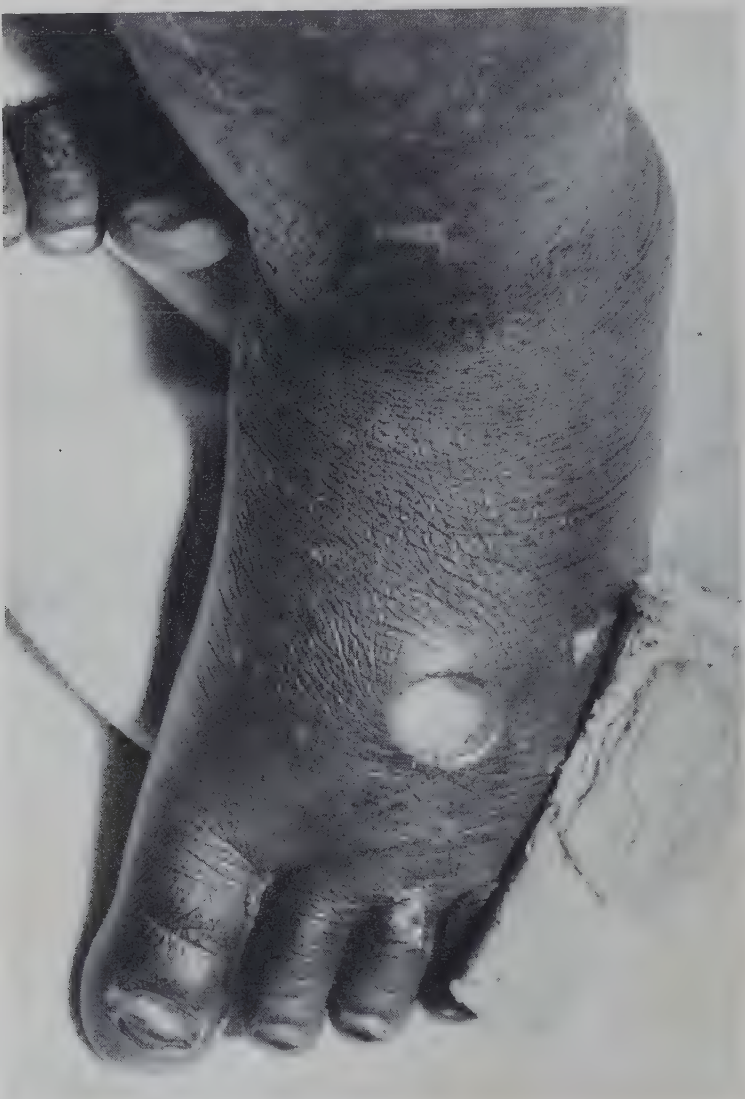


FIG. 9.—Circular ulcer on dorsum of foot in kwashiorkor. Not syphilitic. Note the absence of reaction round the edge of the ulcer.

a resemblance to the crazy pavement of an English garden path, and the term " crazy-pavement dermatosis " might be reasonably used, if it had not been applied originally to the " enamel-paint " plaques. When the oedema eventually disappears, wrinkled but essentially unaltered skin is left, with no more than deepened skin creases to mark where the white lines used to be. Desquamation s very slight and is confined to the most superficial layers, the skin nderneath being normal in colour and in texture.

Another lesion is occasionally seen. On the dorsum of the foot, r occasionally on the buttocks, or on sites not obviously related o conditions of pressure or movement, a large bulla may form nd burst to leave a shallow erosion (Janssen and le Roux, 1950a). The bulla may precede the circular ulcers which sometimes occur n the same positions. These ulcers may be deep and "punched out", and perhaps 2 centimetres in diameter. The edge is not discoloured, and there is no inflammatory reaction (Fig. 9). A pemphigoid syphilide might be suggested, but this tends to affect he palms and soles, areas which are spared by the bullae of acute kwashiorkor.

There is no doubt that in advanced kwashiorkor the skin is much more easily damaged than normal skin. Bony points, especially on he pelvis, are easily rubbed raw and fingers which are habitually sucked can lose skin to an astonishing depth, and become completely white and soggy. Eyelids which are forcibly closed by oedema may develop raw edges. The liability to injury raises great difficulties n balance experiments on young children, who have to be held in position for long periods for the collection of their stools and urine. t was found at Kampala that only if the utmost care was taken to distribute pressure evenly, and thick spongy rubber was used at every corner, could the skin be prevented from breaking. It was noticed that any hard rim or edge in contact with the skin for more han an hour or two would produce darkening much like that of he "purple patches", and that if the contact was allowed to con-inue, a blister would form. In one or two instances, where the child's skin was thought to be in such good condition that there was no possibility of it breaking down, it was found at the end of the balance period that some discoloration had occurred, although the kin looked quite healthy otherwise. The discoloration did not disappear for many weeks.

Although rare in Kampala, where infants are weaned on to cooked bananas (plantains), and sweet potatoes, a dermatosis may be seen in ther places which appears similar to that of classical pellagra in dults (p. 117). These pellagroid dermatoses are more frequent where children are weaned on to a diet containing much maize flour; they are common in Johannesburg (Gillman and Gillman, 1951); Rhodesia (Gelfand, 1946) and Italy (Frontali, 1953). It is possible that they are more frequent during the spring, in dry areas of the world, where there is much seasonal change of sunlight, wind, and temperature, and a dry atmosphere, all of which act as predisposing factors, and that they are rare in tropical climates, except in highland areas. They occur on the back of the hands and on the extensor surfaces of the lower arms, the back of the lower legs and the dorsum of the feet, the bridge of the nose and the nape of the neck. Acute bullae may form, but are rare. More commonly there are dry, rough areas of hyperpigmented skin ; these may desquamate, but the desquamation is not so marked, or so spontaneous, as in the " enamel-paint dermatosis " which affects most typically the napkin area in cases of kwashiorkor. At the same time as these pellagrous dermatoses occur on the limbs, there may be a fiery-red stomatitis and much increased salivation, but these signs are not often seen with the " enamel-paint dermatosis " of acute kwashiorkor in tropical regions. The stomatitis and pellagroid dermatoses are said to respond rapidly to *small* amounts of nicotinic acid (Frontali, 1953) —large doses can be rapidly fatal (p. 179)—but to respond only very slowly to skimmed milk powder, which heals very quickly the erosions caused by the " enamel-paint dermatosis " of kwashiorkor.

Although on grounds of general appearance, distribution, and response to treatment, a distinction can usually be made between the pellagroid dermatosis and the " enamel-paint dermatosis " and between them and " crackled skin " and " mosaic skin ", yet all stages and intermediate grades can be seen. All the manifestations appear in response to irritation by pressure, or the trauma of weather or sunlight, and all tend to accumulate pigment in glazed plaques, and to desquamate.

In races having naturally little pigment in the skin the areas of hyperpigmented " enamel-paint dermatosis " may appear as " coffee stains " ; the generalized hypopigmentation may not be noticed, although attention should be paid to any undue pallor of the skin. Generalized hyperpigmentation, resembling that seen in Addison's disease, has been reported in white children (Carvalho, 1947 ; Frontali, 1953). The pellagroid changes described above in dark-skinned children may also occur in those with fair skins.

In Kampala, the nails are sometimes thin and soft, but the changes are not very marked. In Mexico City, on the contrary (Cravioto, 1953, personal communication), the thinness of the nails is very obvious and shows particularly when healthy new nails start to grow, orming a mass at the nail base that is completely separated from the ld nail. In Guatemala the nail bed is frequently distorted by a hickening resembling that caused by a fungus infection (Behar, 953, personal communication).

7. *The digestive system.* In kwashiorkor, the mouth and tongue nay show signs suggesting vitamin deficiencies. They are perhaps nost often found in the terminal stages of advanced cases and are iscussed later. Of much greater importance is the decrease in the ppetite. In the very ill children the appetite is poor or is lost comletely, and all foods may be actively repulsed. Many authors have poken of the special measures they have adopted to get the children eat. At Kampala, it is not usual to persist in attempts at feeding he child in the normal way, if there is continuous refusal: the feeds re made liquid and are given by gavage. Vomiting is usually a sign hat unsuitable foods are being given. Some authors have reported high incidence of vomiting, but it is seldom so severe that it produces dehydration.

It is characteristic of the advanced form of the disease that the tools change with every alteration in the diet, as though the normal ntestinal processes are in abeyance, and bacterial action, which is sually such an effective leveller of the gut contents, is being greatly nodified or to a large extent suspended. It is very soon obvious, any experimental feeding is tried, that fats are badly tolerated, and hat a great deal of carbohydrate, especially if it is starchy or fibrous, scapes digestion. A careful naked-eye examination of the stools eveals small and large particles of food which can nearly always e recognized for what they are; cooked bananas, for instance, merge apparently unaltered and have been mistaken by more than ne child for food. This is not so incredible, and is a little less isgusting, if it is realized that the stools may have no faecal smell, s well as looking nothing like a normal stool (*cf.* Williams, 1938b). articles of food are more difficult to recognize if the child is fed on ruels and milk.

If full cream milk is given there will probably be a brisk diarroea, most likely caused by the fat, and a few curds may be seen the stools. If skimmed milk is given, it will be well tolerated long as the amount of lactose is kept below a certain limit, but that is exceeded, there may be diarrhoea caused by the sugar . 187). The stools will then be strongly acid in reaction, and will watery, with flecks of soft yellow material, irregularly stained green. Microscopic examination shows great numbers of cells, which have apparently come from the intestinal wall, but with few if any polymorphonuclear cells and no erythrocytes. In several instances, culture of such stools has produced almost pure growths of *Streptococcus faecalis*, and very few coliform bacilli.

If the amount of sugar in the diet is reduced, or if the carbohydrate is given in the form of sweet banana (p. 193), the stools usually become formed within a few hours, and their reaction changes to alkaline. An injudicious increase in one of the foods known to be badly tolerated shows at once in the return of the diarrhoea. The sensitivity is so great as to be almost diagnostic.

These observations strongly suggest a failure of pancreatic function, and evidence for such a failure has been found. Duodenal enzymes (p. 169) are reduced in activity, and nitrogen balances (Table 10, p. 200) show that much protein escapes absorption. These facts have been utilized in the development of suitable diets for treatment.

Experience at Kampala shows that whether or not diarrhoea occurs in a child with kwashiorkor depends on the degree of severity of the disease and the extent to which digestive function is impaired, on the kind of food that the child is given, and on his appetite for that food. At Kampala, long-continued diarrhoea is not often reported as being an important feature of the history of the child before he is brought to hospital, although short attacks seem to be fairly common, but Bergeret (1948) said that a severe diarrhoea lasting several weeks was often mentioned. Achar and Benjamin (1953), who found diarrhoea very frequently, decided that it was often related to past attacks of dysentery, usually of bacterial origin, and 25 of the 40 children investigated by Jayasekera *et al.* (1951) had had diarrhoea.

Any conflict in reports of the frequency or absence of diarrhoea could probably be reconciled if full details of the diets were known. The bulk of the diets is starchy carbohydrate, which escapes digestion more and more as the disease progresses. Certain forms of carbohydrate, such as those in the sweet bananas and plantains that form much of the home diets of Kampala children, do not appear to provoke diarrhoea as easily as other foods. It is possible that certain diets such as those which contain much cane sugar, as in the West Indies, or much maize meal, as in South Africa, may provoke more diarrhoea, and that diarrhoea is an important factor in producing the in and desiccated cases seen in those countries. In any country, is a serious sign and increases rates of mortality. The rarity of arasmic or 'atrophic' cases of kwashiorkor in Kampala may be lated to the rarity of persistent diarrhoea.

The examination of the abdomen by manual palpation is less nportant than a consideration of the changes in the stools. In oite of the poor intake of food, the abdomen is usually prominent, not tense and distended. This probably reflects the poor digestion food, and its gaseous decomposition, and reduces the amount of ood that can be taken with comfort at any one time. The liver may e displaced upwards, and the palpation of its edge may be made ifficult by the distension of the abdomen, but it may descend and ecome more easily palpable if the abdomen is empty and the anterior odominal wall is relaxed, as in any state of dehydration. Only in hildren in whom the disease is far advanced, and who are very norexic, or having much diarrhoea, is the scaphoid abdomen seen.

8. *The Liver.* Reports of kwashiorkor do not agree about the ze of the liver. It is necessary to point out that in the new-orn child, and up to at least the end of the first year, the liver normally palpable well below the costal margin. Later, by the rocess of differential growth, the liver does not enlarge so rapidly the rest of the body, and the edge gradually recedes. A well-own child who is 6 months old may weigh 7·0 kg. A badly-rown child who is 2 years old, such as many who suffer from washiorkor, may weigh the same. His liver may be the same size, nd just as palpable, as that of the other child, but it can hardly be id to be enlarged.

At Kampala, the liver is not enlarged in the uncomplicated case, cording to the above criterion. It is the right size for the age the child, and does not account for an unusually large proportion the total body weight (Davies, unpublished results). Gillman nd Gillman (1945a) and Altmann (1948) in South Africa, and aterlow (1948a) in the West Indies, have been amongst the authors ho stressed the enlargement of the liver as an important sign. In e Kasai, Pieraerts (1952, personal communication) found that e livers were no larger than those at Kampala, but at Katana on ke Kivu, also in the Belgian Congo, one of the present writers . F. A. D.) found enlarged livers in three of four children who ere apparently suffering from kwashiorkor, and the doctors at Mission hospital where these children were seen said that some enlargement was usual although gross enlargement, of the degre shown in Fig. 10, was unusual. Another of the writers (H. C. T. has seen children with enlarged livers in Nairobi, Johannesburg Accra, and at Ibadan in Nigeria. Exact information about th weights of the livers in childre in these places would be mos valuable.

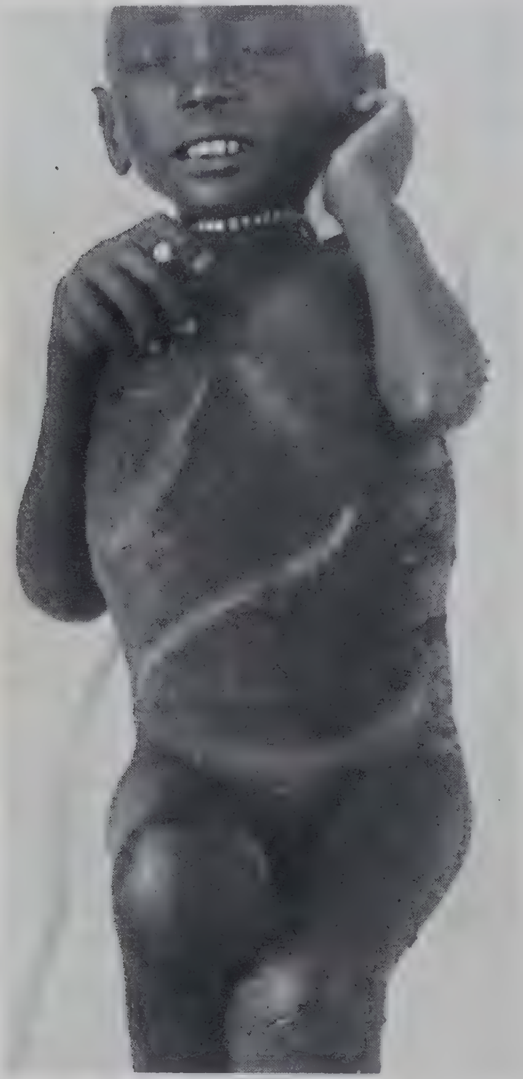


FIG. 10.—Enlargement of the liver, of which the edge has been marked with chalk. A fatal case, seen near Costermansville (Belgian Congo).

Whether the liver is enlarge or not during life, biopsy reveal that it is almost always fatty The enlargement may depen upon the degree of fatty chang which varies from one case t another, and may occur only a a certain stage of the illness

9. *Mental changes.* Broc and Autret (1952) make the comment that although the menta apathy of kwashiorkor is wel known, it has apparently been so much taken for granted tha it has been left out of most descriptions. Trowell (1937) stressed the apathy and misery and discussed the resemblance to pink disease (acrodynia). Clark (1951a) went so far as to say that he believed the mental changes to be the most constant, and probably one of the most important, of the changes which occur in the disease.

Even those children who are not severely ill are remarkably silent and still. They sit where they are put, and although they may be well able to walk, never seem to want to do so. They have lost all the normal curiosity and desire for exploration that is natural to a child. If their general condition is worse, they are hopelessly apathetic. Their faces are dull and expressionless, the only emotions they show being resentment or pain. They have no interest in their

roundings, their food or, as far as can be judged, in anything
e. They lie in wet and dirty beds without protest. They resent
y disturbance with an intensity that makes them come suddenly
ve: they cry if they are strong enough, or moan if they are weak.
the terminal stages they are almost comatose. If they are raised
m the bed they try to crawl back, and to cover their heads with
e bedclothes. They seem to seek not only warmth, but the
mfort of darkness almost as though they had a true photophobia.
renewal of interest is one of the most obvious signs of improve-
ent and the child who smiles is well on the way to recovery. The
meanour is probably the best single clinical guide to the degree
severity of the disease.

10. *The cardiovascular system.* Clinical and X-ray examination
the heart in kwashiorkor, even when the disease is far advanced,
ver reveals any striking abnormality. At Kampala, there is no
idence of congestive heart failure; because the neck is thin, the
ck veins are usually obvious, but they are not distended unless
e child is crying. The liver, even if enlarged, is never tender
d does not show congestive changes at autopsy. Although
ght degenerative changes are sometimes present in the myo-
rdium (p. 153), nothing has been found which disturbs the clinical
pression that heart failure plays no part in causing oedema. It
possible that extreme anasarca might be an intolerable embarrass-
ent in a few of those cases which are said to be in urgent need of
uretics (p. 178), but such cases must be very rare.

Gopalan (1953, personal communication) has found that in some
es the pulse-rate is slow, as it is in hunger oedema in adults. It is
uch more usual, however, for the rate to be slightly raised. It
not irregular. Janssen and le Roux (1950a), and Dricot, Beheyt
d Charles (1951) have made electrocardiograms, but the changes
ected do not seem to be very striking. There was generally low
plitude of the QRS complex and the T wave, and very often slight
normalities which were thought to be of no great significance.
ese changes did not respond to treatment by thiamine. de la
rre, Berber and Duran (1949) studied electrocardiograms taken
n Mexican children diagnosed as suffering from "third-degree
lnutrition" in some of whom there were also neurological changes
gesting a thiamine deficiency. Nearly all the children gave
ormal tracings at the beginning of treatment, but most of the
ormalities disappeared when the children recovered. The rate

of recovery did not seem to be accelerated by thiamine. On the other hand, Frontali (1953) has reported cases of *distrofia da farine* in which he thought there was some cardiac involvement caused by thiamine deficiency : the involvement showed in small abnormalities of the electrocardiogram. He also described changes in the electrocardiogram that seemed to be associated with a low level of serum potassium, as they were abolished by giving potassium salts.

11. *Changes in the blood.* In uncomplicated cases of kwashiorkor it is not possible to detect any pallor of the mucous membranes, and anaemia does not contribute to the pallor of the skin. There is, nevertheless, usually a moderate degree of anaemia. Normocytic anaemia is the form most commonly seen at Kampala and also near Johannesburg, where Altmann and Murray (1948) found it in 25 out of 32 cases. In four of their cases the anaemia was microcytic (Mean corpuscular volume less than 80 c.μ) ; this kind of anaemia is rare at Kampala (Trowell, 1937), but seems to be more common in the Philippines (Stransky and Dauis-Lawas, 1950a) and in India (Chaudhuri, 1950). The remaining three of Altmann and Murray's cases had a macrocytic anaemia (Mean corpuscular volume over 95 c.μ).

A macrocytic anaemia, with a colour index of unity, sometimes occurs at Kampala (Trowell and Muwazi, 1945) and has also been reported to be common in Curaçao (Van Der Sar, 1951). All the varieties of anaemia may have somewhat low values for mean corpuscular haemoglobin content. According to Dricot, Beheyt and Charles (1951) the essential change in the children (aged 6 to 15 years) they investigated at Leopoldville was not a simple increase in mean corpuscular volume but an increase in the mean diameter of the cell and a shift of the Price-Jones curve to the right. Recent work by van Oye (1953, personal communication) suggests that in the anaemias of kwashiorkor found at various centres in the Belgian Congo, the red cells are similar to those described by Larsen (1948) as being typical of liver disease—cells of normal volume, with increased diameter but decreased thickness. Cells of this kind were detected in the anaemia of pregnant African women (Woodruff, 1951, 1952 *Proc.*) and their presence was attributed to disturbances in liver function and to protein malnutrition. It seemed reasonable to expect that they might occur in kwashiorkor.

Very little work has been done on the bone marrow ; true megaloblasts of Ehrlich and the *Stabzellen* of pernicious anaemia e sometimes found (Altmann and Murray, 1948); haemato- iesis is usually normoblastic, but occasionally macronormoblastic rowell, 1951b). Lambrecht and Holemans (1953) were unable to etect any abnormal types of erythropoiesis in the bone marrow of eir cases. They considered that the ratio of leucopoietic cells to ythropoietic cells was greatly increased in the more severe cases d that the increase was a guide to prognosis. They did not find ch a large increase in children who were severely anaemic from lminthic infestation, and thought that the state found in the ildren with kwashiorkor could be explained by prolonged protein arvation. The bone marrow of a child severely ill, but with a rmal ratio, might retain its ability to respond to therapy: if the tio was abnormal, the ability to respond might be lost. Lambrecht d Holeman's findings are unexpected, and should obviously be nfirmed as soon as possible.

When a child is admitted to hospital at Kampala there is nearly ways a slight reticulocytosis and a thin stained film shows aniso- tosis and some polychromia. There may be slightly hypochromic acrocytes and normocytes, especially if the anaemia is more severe an is usual. Some of the red cells may be vacuolated, and target lls may be seen.

Since it is generally admitted that even with the most modern d refined methods of examination the diagnosis of an anaemia ust often depend on its response to treatment, it may be mentioned re that although a markedly hypochromic anaemia accompanying ashiorkor, whether normocytic or microcytic, responds well to n, the other varieties of anaemia do not respond to folic acid, amin B_{12} or liver extracts (Pieraerts, 1949a, 1950b; Wills, 1951, rsonal communication). Altmann and Murray (1948) and Altmann 950) reported that treatment by milk, which was successful in using general improvement of the child's condition, often brought eeble reticulocyte response which, however, was seldom followed a significant rise in red-cell count and haemoglobin. It has not en possible to confirm this reticulocyte response to milk protein cases treated at Kampala. The haemoglobin, and the red-cell unt, may respond occasionally to iron.

In tropical regions many children with kwashiorkor have also pical infections, certain of which may destroy blood very rapidly. laria is a common complication in Uganda; hookworms are very nmon but do not often cause severe anaemia until after the second year. Children in the third, fourth and fifth years of age who apparently have both hookworm anaemia and kwashiorkor are sometimes seen in Kampala, but after the fifth year and as the incidence of the nutritional disorder decreases, so does the helminthic disease appear to increase in relative importance. Tuberculosis may also complicate cases of kwashiorkor. In the presence of the infections the anaemia may become severe, and if a very low haemoglobin is detected in any case of kwashiorkor the presence of an infection should be suspected. If specific therapy for the infection is employed there is usually a prompt response of the red-cell count, of the haemoglobin and of the reticulocytes. Cases that are complicated by many hookworms often develop a severely hypochromic anaemia ; if iron is then given a reticulocyte response occurs and the haemoglobin improves. The reticulocytes which arise in the treatment of these hypochromic and infective anaemias are often large, so that if they are produced in sufficient numbers, their presence may cause an anaemia which has been normocytic to become temporarily macrocytic (Lehmann, 1949 ; Trowell, 1948–49, 1951b).

Cases of kwashiorkor are frequently seen at Kampala in which there is no evidence of active malaria on admission ; thick blood smears, even if most thoroughly searched, reveal no malarial parasites. There is however often a history of recent attacks of " fever " —most probably malaria—there may be splenomegaly, and a liver biopsy often reveals malarial pigment in the Kupffer cells (Trowell, 1948–49, and see p. 130). It is doubtful if these should be regarded as non-infected cases, in the strictest sense of the word. They often have rather a high reticulocyte count on admission ; some have perhaps undergone a natural remission of the malaria, while in others there may have been treatment by anti-malarial drugs. The haemoglobin is probably improving and the anaemia is either normocytic or macrocytic.

The majority of cases of kwashiorkor occur in young children, in whom lymphocytes are normally more numerous than polymorphonuclear cells. If this is discounted, there seems to be no consistent abnormality in the white cell series. Altmann and Murray (1948) found that eosinophils were often absent or very scanty in children recently admitted to hospital, but experience at Kampala resembles that of Stransky and Dauis-Lawas (1950a), who thought they were variable in number. Gomez, Frenk and Galvan

1), however, consistently found an eosinophilia, which was test when the child was first admitted to hospital, and lessened ng treatment. Because a recent attack of malaria is such a fre- nt complication in cases admitted at Kampala, monocytes, often aining malarial pigment, may be seen and there is sometimes a openia. Platelet counts were said by Chaudhuri (1948) to be nal, but prothrombin time, and plasma fibrinogen, were found e slightly raised by Jayasekera *et al.* (1951). Bleeding and gulation times were found to be normal by Dricot, Beheyt and rles (1951) and by Caruana, Hamza and Ghileb (1953); the hors last named, who worked in Tunis, and Gomez in Mexico (1953, personal communication), have noticed an unexplained pura that was not, apparently, related to pressure. Didier 53a, b) found that purpuric patches and ecchymoses were fre- nt. Nothing of a haematological nature is known that might ount for these haemorrhagic phenomena. Some are apparently ninal, and may be the results of an overwhelming infection. ey are rarely seen in Kampala.

So far, apart from the question of infection, it has not been pos- e to correlate the appearance of the different kinds of anaemia ch accompany kwashiorkor with the severity of that condition, the diet, with the age of the child, with climatic conditions or any other factor. The most likely cause of the essential emia is perhaps protein malnutrition, which is known to cause ewhat similar effects in experimental animals.

It is very difficult to decide whether there are different varieties naemia in uncomplicated kwashiorkor. It is unsatisfactory to ulate local factors, which differ from locality to locality, or even member to member of the same community. At Kampala the ur index even in severe cases of kwashiorkor is usually unity ightly over unity (Trowell, Davies and Dean, 1952), a point of rentiation from the anaemia of hookworm disease. Gastro- tinal diseases, such as coeliac disease, sprue, intestinal tubercu- and stricture, are often accompanied by an anaemia which is ble not only in degree but also in character, the size of the red being one variant. The comparable state of affairs present washiorkor is not a unique anomaly even if it lacks a clear nation.

2. *The urine.* Williams (1931–32), Russell (1946), Chaudhuri) and Janssen and le Roux (1950a) are among the authors

who confirm the Kampala experience that albuminuria very often accompanies kwashiorkor. In Uganda and elsewhere the presence of albuminuria does not seem to be correlated with the severity of the disease ; blood cells and casts are very seldom found in the urine, and urinary infections are uncommon. In Guatemala, Flores (1947) found erythrocytes and casts, and a trace of albumen, fairly frequently, and Gomez in Mexico City (1953, personal communication) found not only erythrocytes but also casts in about 15 per cent of his cases, and leucocytes in almost 95 per cent. All the cells, and the casts, disappeared from the urine when the children recovered. In Gomez's experience, albuminuria was rare.

Whenever the albuminuria has been reported, it has been said to be very slight. Its presence or absence is not mentioned in many accounts of the disease, and it is possible that it has sometimes been missed or mistaken for the albuminuria of nephritis. A few writers (for example, Gillan, 1934–35, and Achar, 1950) specifically deny that it occurred in their cases. The significance of the albuminuria is unknown (see p. 222).

13. *Other signs of malnutrition.* In a condition such as kwashiorkor, where there is so much disturbance of digestion and of intestinal flora, it is to be expected that signs of vitamin deficiencies may be found. The diets which have given rise to the disease may be deficient, not only in protein but in vitamins as well, and the anorexia causes a decreased intake of all nutrients. It should also be borne in mind that certain vitamins, notably some members of the vitamin B complex, are intimately concerned with various aspects of protein metabolism. They may normally combine with protein in enzyme systems, but the combination may not be possible if severe protein deficiency is also present. If, as is nowadays believed, the amino acid trytophan is normally an important source of nicotinic acid, a shortage of the amino acid may lead to a shortage of the vitamin. A deficiency of protein may therefore in theory produce in more than one way signs suggestive of vitamin deficiencies, and the signs may disappear after the amount of protein in the diet has been increased.

The signs of vitamin deficiencies which often occur in advanced cases of kwashiorkor were at one time regarded as essential features of the disease, until it was realized that they are inconstant. There is much to suggest that the signs vary from place to place according to the different diets employed ; a maize diet, for instance, may ovoke an attack of pellagra. The relationship of the different rmatoses of kwashiorkor to pellagra is discussed elsewhere (p. 118).

There are also signs that might be attributed to ariboflavinosis ughes, 1945–46). Sodden areas occur at the corners of the outh; they are probably distinct from the bleeding fissures which cur in the same region (p. 91). Other sores appear at the ter canthus of the eye, in the naso-labial fold and around the rders of the anus, vagina and prepuce, and later there may be perficial fissuring or ulceration. The lips may lose their pigment, come red and raw, and develop vertical cracks. The tongue y become bare and rose-coloured or magenta (Altmann, 1948) d its papillae may enlarge, giving a granular appearance. There y be blepharitis, but circumcorneal injection has only been scribed by Turnbull (1951: see below) and then as part of a ghly complicated syndrome; the simulation of photophobia 101) is probably of mental origin. There may be vaginitis or lanitis, but these are rare unless the dermatosis has involved the rineum or scrotum. Riboflavin is said to heal some of these ions, but Carvalho *et al.* (1945) and Hughes (1945–46) imply that majority of the children die unless satisfactory dietary therapy is en as well.

The clinical data seldom suggest any deficiency of thiamine. stellanos (1935) in Cuba was one of the early writers who conered that the disease of kwashiorkor might be a mixture of lagra and beri-beri, but the administration of thiamine, orally parenterally, is of no benefit and may even be injurious (Gillman l Gillman, 1946). Thiamine does not usually help to remove the lema or abolish the slight abnormalities in the electrocardiogram 101), nor does it improve the weakness of the limbs. Its inectiveness is an argument against the possibility that a true ipheral neuritis is present. While this has been the experience workers in Africa, Frontali's experience in Italy (1953) has been erent (p. 102). It is hoped that he will carry his investigations her.

The possibility that deficiencies of protein and of several vitamins occur together cannot be denied. Turnbull (1951) described ndrome found in Mexican children which he believed to be a ltiple-deficiency disease. Most of the children were aged from 2 years, and the maximum incidence was towards the end of the ond year. There was oedema, unexplained shadows in X-rays of the lungs (p. 77) and changes in the serum proteins of the kind found in kwashiorkor : fat was found every time a liver biopsy was done, the bromosulphthalein test was usually negative, but the thymol turbidity and cephalin flocculation tests were often positive. The amount of esterified cholesterol in the serum was usually below normal.

So far, the description fits kwashiorkor. In addition, however, Turnbull mentions

(*a*) a dermatitis starting on the dorsal parts of the hands and feet and extending later to other parts of the body, stomatitis and glossitis, and psychic disturbances (confusion, disorientation and fear),

(*b*) cheilosis, acne of the nose and the surrounding area, conjunctivitis and circumcorneal injection,

(*c*) electro-cardiographic changes, and changes in the electrical responses of the muscles, of the kind found in beri-beri, hypotonia and loss of the patellar reflex.

The signs in group (*a*) were thought to be due to nicotinic acid deficiency, and with some reason, since the psychic disturbances responded to treatment with that vitamin ; those in group (*b*) were considered to show riboflavin deficiency, and those in group (*c*) to show thiamine deficiency, especially because the thiamine excretion was very low.

Turnbull treated his cases with protein and with vitamins simultaneously. The part played by each of the supposed deficiencies could only have been discovered if he had been able to give one therapeutic substance at a time.

In all the severe cases of kwashiorkor at Kampala in which estimations of the blood carotenoids have been made, the values were very low, some being under 10 per cent of the values found for European children (Moore and Sharman, 1951 ; Trowell, Moore and Sharman, in the press, and see Table 6, p. 173). The children with kwashiorkor occasionally have slight xerosis and xerophthalmia, but Bitot's spots have not been seen. These and other manifestations of a deficiency of vitamin A are more common in India, Indonesia and Mexico. Oomen (1953, personal communication) found a puzzling combination of ocular signs and kwashiorkor in Indonesia ; the home diets of the children seemed to contain adequate amounts of carotenoids, and there was no correlation between the degree of ocular involvement and the severity he general condition. Achar and Benjamin (1953) detected ar signs which they attributed to vitamin A deficiency in 44 per of their cases of kwashiorkor; the signs included dryness and ration of the cornea, xerosis and keratomalacia, and a peculiar ldy colour of the gutter between the sclera and the lower lid. re was no accompanying phyrnoderma, but the apparent divorce veen eye and skin signs of vitamin A deficiency has been noted ny times, and the skin signs are known to be comparatively rare nfancy. In Mexico, Pagola (1948) employing the bio-corneal lamp microscope, found diminished humidity of the cornea in per cent of the eyes he examined, xerophthalmia with ulceration per cent and Bitot's spots in 1 per cent. Dark adaptation seems here to have been measured, although that should be possible hildren of the older age groups, and might be of interest as an y diagnostic test.

There has been little enquiry into the manner in which so severe duction in the amount of vitamin A might occur in the body, there is much to suggest widespread changes in the mucous mbrane of the small intestine in cases of kwashiorkor (p. 149), the liver is fatty. There are, therefore, lesions which may rfere with the absorption of carotenoids and their conversion vitamin A.

Except for one or two doubtful cases, rickets has never been in any African in Kampala, and the small stature of children kwashiorkor, and their backward skeletal development, cannot ascribed to a vitamin D deficiency. The home diet of the dren can contain little of the vitamin, but an adequate supply resumably maintained by the irradiation of ergosterol in the skin. the other hand, in countries where rickets is common, such as th Africa (Altmann, 1948), it may complicate kwashiorkor. ause growth is retarded the degree of rickets is unlikely to be re.

Although it has seldom been specifically reported, a deficiency scorbic acid may arise in association with kwashiorkor (Stransky,), especially in children who have been weaned at an early age o an unsuitable cereal diet. Petechial haemorrhages have been in the later stages of the disease in Egypt by Hanafy (1948), ndia by Achar (1950) and Chaudhuri (1952) and in Tunis by er (1953a, b). In Chaudhuri's cases the level of ascorbic acid e blood was normal. Capillary fragility has not been measured.

Attempts to explain other features of the disease as vitamin deficiencies have been made tentatively. Thus Hughes (1946) considered that the dyspigmentation of the hair might be due to a deficiency of pantothenic acid, but therapeutic trials were inconclusive. Peña Chavarría, Saénz-Herrera and Cordero-Carajal (1946) thought that biotin possibly accelerated the growth of normal hair. The degenerations in voluntary and cardiac muscle (pp. 153, 155) have suggested a lack of vitamin E, and estimations of tocopherols in plasma showed low levels (Trowell, Moore and Sharman, in the press) ; the significance of the low levels is, however, uncertain.

The relation of the 'animal protein factor', vitamin B_{12} and choline to kwashiorkor is discussed on p. 180.

Signs in mild cases

The exact definition of any state of undernutrition is a matter of great difficulty, and the impression gained from reading a long and well-documented review of the subject, such as that of Sinclair (1950), is that although some of the severer states may be susceptible to objective measurement, the milder states can be assessed only by clinical methods, which are necessarily inexact. This is certainly true of kwashiorkor ; the severe case is unmistakable, but the mild case shows few of the immediately obvious signs of ill-health.

The inspection of a hospital population, or of hospital records, may give very little idea of the true incidence of mild cases. Most hospitals in places where kwashiorkor is seen are too overcrowded to permit of the admission of children who are not seriously ill. The amount of interest taken in the disease by a hospital staff determines very largely the total number of children, and therefore the number not severely ill, who are presented for treatment, and the feeling in the hospital that severe cases are beyond reasonable hope of recovery and should therefore not be admitted may limit admissions to mild cases. Striking instances of both these factors influencing in opposite directions the population of children's wards have been found in East Africa, and could undoubtedly be found elsewhere.

It is likely that the true incidence of mild kwashiorkor will not be known until welfare clinics have been greatly extended. In her clinics in the vicinity of Kampala, Welbourn (1951) found a falling-off in growth, and a general tendency towards a deterioration in health, in children during the second year of life. A more critical

mination of these cases suggested that nearly half of the children
nding child-welfare clinics near Kampala might suffer from mild
shiorkor (Welbourn, 1953). Hanafy (1947, 1948) and Oomen
53) were other authors who considered that the comparatively few
es seen at hospital were greatly outnumbered by the milder cases
did not appear there. Mild kwashiorkor is common in certain
ts of the Congo and Central America (Autret, 1953, personal
munication).

Children with mild kwashiorkor are likely to show the following
ns :

1. A failure of normal growth, affecting especially weight and height for age.
2. A decrease in physical activity and in mental liveliness; in simple terms, a lack of normal inquisitiveness and naughtiness.
3. Dyspigmentation of the hair, especially at its tips. This may be recognizable only in children whose hair is black.
4. Episodes of vague ill-health, loss of appetite, and gastro-intestinal disturbance, increasing in frequency and severity.
5. A tendency towards general improvement when a diet rich in protein is given. Alternatively, a tendency towards deterioration, and even the appearance of diarrhoea and oedema, if a poor diet containing little protein is continued.

It was along these lines that Williams (1938a), Purcell (1939)
Russell (1946) recognized the prevalence of mild kwashiorkor
the Gold Coast, coming to their conclusions after observing
dren at centres outside the hospitals as well as inside them.
ey were unable to propose any objective tests for distinguishing
ween mild and severe cases, and this is obviously a difficult
ject, for which even the knowledge of today is insufficient.
tle correlation has been noticed at Kampala between the bio-
mical findings and the clinically-estimated degree of illness, and
oedematous and non-oedematous children (aged 6 to 15 years)
estigated by Dricot, Beheyt and Charles (1951, see p. 178) all
wed essentially the same abnormalities of liver function and of
um proteins. There was perhaps some relationship between the
ount of reduction of the serum albumen and the amount of
ema—a relationship which has been found at Kampala (p. 165)—
not much else.

The response of all cases of mild kwashiorkor to a diet rich in protein is fundamental to establishing the diagnosis. At the present time the most reliable and the cheapest method of applying this therapeutic test is to add powdered skimmed milk to the diet. It is important to exclude cases of undernutrition in which the mere increase of food, or more meals, corrects all the signs of illness and of unsatisfactory development. Thus, if children in the second year of life and receiving a little breast milk take only two meals a day, and those meals are composed largely of a single bulky staple food, it should not be assumed that the suboptimal weight is explained by the presence of mild kwashiorkor. It would appear necessary to serve the same food, cooked in an appetizing manner, at least twice more at other hours of the day. Only after appetite has been fully satisfied and growth remains poor, should kwashiorkor be suspected and skimmed milk powder be added to complete the therapeutic test.

It is also desirable to exclude from the diagnosis of mild kwashiorkor all children in whom an infection may explain unsatisfactory growth. Unfortunately, in the Tropics, in any survey which is conducted to detect the incidence of mild kwashiorkor, a number of children may be found whose growth is unsatisfactory, and in whom there is chronic malaria, a helminthic disorder or some other infection. It is very difficult to decide in any one case how far infection, underfeeding or an inadequate intake of protein, has been responsible. If the cases are sufficiently numerous and can be divided into enough groups it may be possible to evaluate various types of treatment (Doucet, 1952).

It is indeed unfortunate that dyspigmented hair is so often believed to indicate the presence of mild kwashiorkor. It is most unwise to rely unduly on any single sign in the diagnosis of malnutrition of any kind, for very few of the signs are restricted to only one deficiency disease. There are many causes of dyspigmentation of the hair ; for instance, certain diseases in which there is a disturbance of protein metabolism, such as kala-azar (Fendall, 1952), hookworm anaemia, and cirrhosis. Exposure to strong sunlight and oxidizing agents may cause some bleaching, so that healthy Africans, especially if they are sea fishermen, may have hair which is light at its ends (Platt, 1952 *Proc.*). In all these circumstances the hair may become brown, but there is no loss of the normal wiry texture. A few Africans in East and West Africa have carrot-red hair all their lives.

enever mixture has occurred with other races whose hair is not k, the coloured offspring may have a brown tint to the hair; Cape Coloured group of South Africa, and various communities South America, are good examples. Colour of the hair is not, efore, an infallible guide to the presence of mild kwashiorkor.

MORTALITY, THE MODE OF DEATH AND A NOTE ON PROGNOSIS

lortality

All the early writers stressed the very high mortality found in s of severe kwashiorkor. "The disease is always fatal unless ted very early" (Williams, 1931–32); the child "nearly always " (Procter, 1926–27). Here is a clear point of distinction from ger oedema, which usually responds quickly to an increase in diet; and the high mortality in some of the early series of cases example, that of Payne and Payne, 1927) is one of the reasons considering that the disease which was reported was indeed shiorkor.

It has already been said that the high mortality rate, even when tment was with whole cow's milk, led some to doubt whether disease was due to malnutrition. Cow's milk appeared the source of protein and a food suitable for an enfeebled digestion; as only slowly realized that the failure of the digestive enzymes lered the digestion of whole milk impossible, and the mortality s of severe kwashiorkor did not drop until powdered skimmed was available. Even then Altmann (1950), who used a skimmed c acid milk, reported a mortality rate of 32 per cent for the eding three years in Johannesburg. In Durban, Klenerman o) noted an appalling death-rate (49 per cent of 727 children), but Walt, Wills and Nightingale (1950), using a special milk aration, lost only 11 per cent of 33 children in the same town. mortality rate in South Africa may be affected by the high lence of 'atrophic' cases (Altmann, 1948), which are said to ery difficult to treat; if they are excluded from any series, and those in which death occurs within 48 hours of admission to ital, the mortality under the best conditions is probably below er cent. Any very high rate, such as that of 35 per cent reported lark (1951a) in Kenya, should nowadays suggest a failure of peutics. At the present time it is impossible to state the true mortality rate in severe kwashiorkor, even with treatment by the best modern methods, because there are no generally accepted objective criteria of severity. Those anxious to investigate treatment systematically will naturally try to exclude complicated cases; they may for various reasons even include many mild cases of kwashiorkor, and it is usually impossible to compare the figures of various investigations. One thing is certain; despite advances in treatment, kwashiorkor still justifies the comment of Brock and Autret (1952) that it is "the most serious and widespread nutritional disorder known to medical and nutritional science".

2. The mode of death

Many of the children who die are admitted moribund and survive only a day or two. They are very feeble, and apathy is replaced by a stupor which deepens into coma, as if the cause of death was hepatic (Hughes, 1945–46; Achar, 1950). Little is known about the mechanisms involved, but at Kampala this manner of dying was at one time common, even several days after admission, in children treated with foods, including whole milk, now known to be unsuitable. Others died after a long period of progressive inanition; usually they had severe anorexia, and lost their oedema, so that their terminal state was one of undernutrition with extreme cachexia overlaying kwashiorkor.

Nowadays, with improved methods of treatment, most of the deaths in cases without an infection occur in one of two ways. A child may, after some days of apparently successful treatment, continue to lose weight far beyond the normal period in which oedema is being removed. The appetite may be fairly well retained, there may be no vomiting, very little looseness of the stools, and no rise in temperature. Nevertheless, there is dehydration, for which there is no obvious explanation. The children get progressively feebler, but remain conscious almost to the end. In one such child at Kampala, a blood urea of over 300 mg./100 ml. was found, but there was no other evidence of uraemia. Another child, whose blood urea also reached a very high level, was rescued by intravenous glucose-saline injections. Other children have been lost even more mysteriously. They have been apparently well on the way to recovery, sometimes after several weeks of treatment, and suddenly, without warning, they have died. One or two deaths occurred soon after a large meal, which gave rise to speculations about the possibility of tal hypoglycaemia, but no evidence for this theory has been nd, at least in infants (but see p. 174). Nothing was discovered ost-mortem examination to account for the deaths, which were umably due to some disturbance of blood chemistry. Sudden hs of this kind have been reported from other centres (Stones, 5-36; Hughes, 1945-46; Waterlow, 1948a; Véghelyi, 1950a; cot, Beheyt and Charles, 1951; Jayasekera *et al.*, 1951; Clark, ra; Sutedgo, 1953, personal communication; Achar and jamin, 1953), but no explanation has been offered. Janssen and oux (1950a) had some children who died with increasing oedema, this has not been seen at Kampala.

Much investigation of electrolyte disturbance, of sodium reten- and of potassium depletion and of many other factors affecting er balance, would probably be needed before the cause of death ll cases could be established.

Death from intercurrent infection calls for little comment, except it has not been uncommon at Kampala to watch a child die n what seemed to be an intractable pneumonia, despite full biotic treatment, and to find at post-mortem no evidence of a g infection. The signs and symptoms were apparently due to d in the lung tissue (p. 77), but the amount of fluid found at opsy was so small that it was unlikely to have been the cause of th.

The prognosis of severe kwashiorkor

Attempts have been made to assess the prognosis in acutely ill ients by studying the severity of individual signs, but they have ved unreliable guides. The degree of the fatty infiltration of liver (Gillman and Gillman, 1945d) or the amount of its enlarge- nt and the impairment of liver function have not proved helpful tmann, 1950). The degree of dyspigmentation of the hair has wn no correlation with the severity of the general condition, ough it is possibly an indication of chronicity, and the anaemia ects most closely some infective complication (Lehmann, 1949). single clinical or biochemical test so far devised has proved of ch value.

A child severely affected by kwashiorkor usually appears very but almost everything depends on the immediate response to therapeutic diet. Nothing has proved so reliable in assessing immediate prognosis as a consideration of the general condition of the child and especially the mental state. Apathy, anorexia and a severe dermatosis mark the terminal stages and are regarded as ominous signs : if they do not improve within a few days of the beginning of treatment, the child will probably die. Intractable diarrhoea and continued loss of weight, accompanied often by the loss of most of the oedema, together producing something approximating to the "atrophic" state of Altmann (p. 68) signify a poor prognosis.

The results of treatment, and the ultimate prognosis, are discussed later.

THE DIFFERENTIAL DIAGNOSIS

Those who have seen children suffering from severe kwashiorkor can recognize the disease at first sight ; it may be much more difficult for those who have never seen an actual case and who rely on written descriptions. The combination of subnormal weight, oedema, apathy and peevishness, and stools containing large amounts of undigested food, is most characteristic and occurs in almost no other disease ; if in addition dyspigmentation of the hair or skin is obvious and has been acquired but recently, the diagnosis becomes more certain ; if the characteristic "enamel-paint dermatosis" is also present there is no further question of doubt.

Differentiation from other oedematous conditions

1. *From renal and cardiac disease.* If oedema is an outstanding sign, other causes must be excluded. Cases of severe kwashiorkor have been described in which there was a generalized anasarca like that found in acute or subacute nephritis. The two diseases have often been confused, which is understandable when it is remembered that the urine in a case of severe kwashiorkor may contain a trace of albumen, some leucocytes, one or two casts, and occasionally even a very few red cells. None of these abnormalities in the urine is ever marked in kwashiorkor, and other signs of this disease are always present ; the signs peculiar to acute or sub-acute nephritis, especially the high blood-pressure, and the sequalae are absent. The blood urea is almost always very low when the child is admitted, and usually rises moderately during treatment (p. 210). At Kampala the distinction between kwashiorkor and nephritis is usually obvious ; the nephritic child may be grossly oedematous, but his hair and

are black and lustrous, and he is not particularly miserable. course of the two diseases is quite distinct, and if the case es to autopsy the appearance of the kidneys will of course decide issue. The oedema present in severe kwashiorkor has seldom confused with that of congestive cardiac failure—a rarity in y childhood. The other signs of failure are absent; the liver, ough possibly enlarged, is not tender and the minor changes in electro-cardiogram in life, or in the sections of the myocardium r death, should never cause any serious difficulty.

2. *From hunger oedema.* The association of oedema with states nalnutrition has been noted for at least two thousand years, and Cance (1951) has recently reviewed the literature, with a far ge into history. True hunger oedema is, however, very rare in dren (Kerpel-Fronius and Varga, 1953), and it is probable that ny of the reported cases of "nutritional oedema" in infancy e cases of kwashiorkor. The older accounts of "nutritional ema" lacked precise description: little was known of the nposition of the diet taken before the onset of the illness, the ical description was inadequate, there were few observations of biochemical changes, and the post-mortem appearances were onclusive.

"Nutritional oedema" is a vague term, and "hunger oedema" better one. In recent years it has been applied to oedema ing in persons, previously well fed, who suffer a reduction in that is generalized and not confined to any one element—a uction of caloric value without an alteration of the proportions he dietary elements. The condition has been studied recently dult American volunteer subjects by Keys, Brožek, Henschel, kelson and Taylor (1950), and in a civilian population by a team he Medical Research Council (1951) in post-war Germany. ne of the important features of hunger oedema have already been tioned (p. 40). Its aetiology is different from that of kwashi- or; it attacks most often a different age group, hunger is an ortant feature, and alterations in the serum proteins are very ll. There are some skin changes, but they are usually slight and nportant, consisting of roughening on the backs of the arms and hyperkeratosis, and fine desquamation of areas that have been matous.

. *From beri-beri and pellagra.* With the history of the recogni- of kwashiorkor in mind, it is of particular interest to discuss the distinction from infantile beri-beri and from pellagra. Any resemblance to infantile beri-beri can be dismissed, as this attacks almost exclusively the very young breast-fed babies of mothers who are themselves suffering from beri-beri (Fehily, 1941, 1941–42). The thiamine content of their breast-milk is low (Concepcion and Dee, 1949). In the East the term beri-beri has been used rather loosely, and in at least one instance children in the second and third years of life who were oedematous were regarded without much question as having " sub-acute beri-beri ". A more critical examination revealed that the disease they were suffering from was not caused by a vitamin deficiency, but was one which appeared identical with *Mehlnährschaden* (Fehily, 1943–44) and was, therefore, at least a close relation of kwashiorkor.

There is much to support the original views of Williams (1933) that a firm distinction can be made between kwashiorkor and pellagra even if there are certain points in common between the manifestations in the skin, and even if they may sometimes occur together. The clinical picture of pellagra in infancy has been described by many writers (Sambon, 1910 ; Snyder, 1912 ; Greil, 1915 ; Knowles, 1915 ; Bloom, 1928 ; Stannus and Gibson, 1934). The post-mortem appearances in pellagrous infants have also been described (Box, 1913a, b ; Galbraith, 1921 ; Greenfield and Holmes, 1939). Pellagra in infancy appears to be seldom fatal, and is not accompanied by oedema and by many of the features present in kwashiorkor.

There are some important differences between the dermatoses which accompany pellagra and kwashiorkor. Firstly, the distribution of the dermatosis in kwashiorkor is totally different from that in classical pellagra. The former occurs on areas specially subjected to continuous pressure, moisture and apposition, such as the napkin area; whereas the latter occurs in exposed surfaces on the face, hands and feet. Secondly, although nicotinic acid may appear in a few cases of kwashiorkor to bring about some improvement of the skin, or mucous membranes, the child will get worse, and usually die, unless a high protein diet is being simultaneously given. (Conversely, kwashiorkor, unlike pellagra, responds well to a high protein diet, and responds without the addition of large amounts of nicotinic acid.) Thirdly, the dermatosis of kwashiorkor occurs only in the worst cases, and is usually to be regarded as a terminal event.

In conclusion, it may be remarked that the literature of pellagra ll of references to an associated chronic deficiency of protein, so the pathological changes which mark the *final* stages of both gra and kwashiorkor in adults might presumably have much ommon. The changes in the liver and endocrine glands in s of chronic pellagra appear similar to those found in chronic ein malnutrition (p. 257).

erentiation from other causes of anaemia

f the oedema of kwashiorkor is accompanied by anaemia the rential diagnosis may be made more difficult, because a severe mia, especially if caused by hookworm disease, may produce a ralized skin pallor in Africans (Lehmann, 1949). The pallor, ever, has a peculiar yellowish tinge which can easily be disuished from the brown of kwashiorkor by anyone with experience. as already been pointed out (p. 102) that in uncomplicated shiorkor there is very seldom more than a slight degree of mia, and that the anaemia is usually normocytic, with a colour x about unity. The possibility that a child with kwashiorkor is ring at the same time from an infection, which may itself cause mia, should be considered if the anaemia is profound ; the t common causes at Kampala are malaria and hookworm, but severe bacterial infection, such as pneumonia, meningitis, a icaemia or (especially) tuberculosis, can also cause an anaemia, etimes very suddenly. In such cases, treatment of the infection usually be followed by rapid improvement of the anaemia, eas the anaemia of kwashiorkor is slow to respond. Sickleanaemia, which is equally refractory to treatment, can be nguished by a consideration of the history and the physical , and an examination of the blood.

he differential diagnosis of kwashiorkor from anaemia cannot liscussed without considering the obvious overlap between ted cases of kwashiorkor and infections (p. 65), especially which disturb the intake, digestion and metabolism of protein. position is much clearer if one accepts the possibility that ion and protein deficiency may occur together, and that inations of the two may give rise to a whole " spectrum " of ses. At one end of the scale is " pure " kwashiorkor, without ion ; at the other is " pure " infection in persons who, for a period before and during their illness, have had a diet adequate to meet their requirements. In between are all the possible bl ings of infection and protein malnutrition. Thus many well children who are infected by hookworms or ascaris have no sympt apart from those caused by mechanical presence of the worm the gut and no signs except the ova in the stools, but others who on marginal diets may develop severe kwashiorkor with or with severe anaemia. In the poorly-fed children the anaemia and signs of protein malnutrition improve considerably if the paras are removed, even if the diet is unaltered. Improvement oc more rapidly, however, if a diet rich in protein is also given.

Differential diagnosis of the skin and hair changes

1. *The skin changes.* The uniqueness of the “ enamel-p dermatosis ” of kwashiorkor has already been emphasized. prompt response of the eroded areas to high-protein diets affords important point of distinction, not only from pellagra but from ot conditions. The plaques and the bullous eruption may sugges syphilide, the angular stomatitis may resemble syphilitic rhaga and the red straight hair may be confused with a syphilitic wig ; it was as a congenital luetic infection that kwashiorkor was of misdiagnosed in Uganda (Muwazi, Trowell and Davies, 19 The serological tests for syphilis are of help in the diagnosis, both diseases may be present in the same patient (Trowell Muwazi, 1945). The differentiation of the erosions of the der tosis from severe infantile eczema, or from scabies, is usually obvio but again it should be borne in mind that kwashiorkor can associated with other diseases. The resemblance of the severe peel lesions of kwashiorkor to burns has troubled more than one nu with fears that a hot-water bottle was responsible.

2. *The hair changes.* Although the dyspigmentation of the h is not necessarily a sign that a child is suffering from kwashiork it seems likely, from a review of the literature, that it does not oc widely except in communities where kwashiorkor is common among children of the most susceptible age. There may be isola exceptions to this rule. In well-fed communities, however, vast majority of children in the second and third years of life h hair of normal colour, whereas in a locality such as Kampala and environs, discoloured hair is seen everywhere. It is against general background that the importance of a single observat must be assessed.

erentiation from pink disease

Pink disease (infantile acrodynia) is most frequent in children
d from 6 months to 2 years, who become very irritable and
erable ; their hands are swollen and seem to be painful, and may
ome raw from desquamation. They develop marked anorexia,
fail to grow ; they may even have diarrhoea, but that is con-
red a grave sign. Nevertheless, the disease is easy to dis-
uish from kwashiorkor. It arises in well-fed children, and no
nection with any state of undernutrition has ever been suggested,
sibly because the known incidence is highest in Australia and
r countries where undernutrition is almost unknown (Cheek,
3). Sweating is a marked and important sign, and the sweat
ds are hypertrophied ; the sweating is associated with the spread
niliarial or sudaminal rashes. The irritability seems to stem from
painful condition of the hands, and the skin of other parts of the
y is not usually affected by the process that leads to desquama-
. Heat is badly tolerated, and there is tachycardia and hyper-
ion. No beneficial dietary measures are known.

erentiation from other causes of diarrhoea

Occasionally the diarrhoea in a case of kwashiorkor is so severe,
o protracted, as to be the chief presenting sign, and differentia-
is necessary from other diseases characterized by loose stools.
washiorkor the outstanding sign is a failure to digest all forms of
. The correct therapeutic diets are well tolerated, but other
s are not. Fibrocystic disease of the pancreas does not imitate
shiorkor, although pancreatic enzymes may be absent from the
denum : the characteristic lung changes are not found in
shiorkor.

The clinical picture, pathology and response to treatment, dis-
uish kwashiorkor not only from fibrocystic disease but also from
ac disease (Gelfand, 1947–48). The loose stools which accom-
amoebiasis, chronic bacillary dysentery and bilharzia can
lly be distinguished by their typical microscopical appearances.
acute gastro-enteritis of infancy not only occurs at an age
r than that at which kwashiorkor is most often seen, but is
lly an acute disease of short duration, with toxaemia, prostration
dehydration, and without changes in the skin and hair.
onella infections also have a short history, in most cases. It

must be obvious, however, that in areas in which there is mu kwashiorkor all children with unexplained chronic enteritis, dur the second and third years of life, should be suspected of hav kwashiorkor until a therapeutic test has excluded the possibility

THE PATHOLOGICAL ANATOMY OF KWASHIORKOR IN CHILDHOOD

1. Introduction

Knowledge of the pathology of kwashiorkor has grown v slowly. Apart from the difficulties that so often interfere w pathological studies in the Tropics, the inability to secure autopsi particularly in children, the rapidity of autolysis, and other hamperi factors, the main adverse factor was the opinion that fatty infilt tion of the liver, the most striking lesion in kwashiorkor, was terminal degenerative condition, which could not account for a of the signs observed during life. It was therefore more reasonal to attribute the signs to the parasites which could so often be foun or to some vitamin deficiency.

Most autopsies were not performed by trained pathologists b by ordinary medical practitioners, and so it is the more to th credit that they should have insisted on the importance of the liv lesions. Thus in 1918 Jamot described from West Africa fa infiltration of the livers of women and children in the disease whi has been called "*daçaga*". It was the most striking lesion : "*foie de teinte générale ôcre foncé*, *est marbré de taches claires qui donnent l'apparance du foie muscade.*" In *Bouffissure d'Anna* Normet (1926, 1928, 1937b ; Bablet and Normet, 1937) describ very accurately the lesions of kwashiorkor, widespread fatty infiltr tion of the liver with patchy fibrosis and areas of lymphatic infiltr tion, rarefaction and hypoplasia of the pancreatic acinar cells, togeth with hydropic degeneration of myocardial fibres. In Africa, Gill (1934–35) described fatty infiltration of the liver with accumulati of the fat at the periphery of the lobule, cloudy swelling and tubul degeneration of the kidney, and he suspected, though he did n establish, pancreatic insufficiency. Williams (1931–32, 1933) com mented on the fatty liver and the intestinal atrophy, but was unab to make detailed pathological studies. Harkness (1935–36) dre attention to the frequency of parotid enlargement, while Vint (193 37) and Trowell (1937) noted the liver changes and the extrer ymic atrophy. Smith (1942–43) mentioned the marked degree of ty infiltration of the liver found in many young children autopsied Lagos, Nigeria: fatty infiltration of the kidneys was also noted.

In 1944, Gillman and Gillman and their co-workers began to blish a series of papers on the pathology of the liver and other gans of malnourished Africans which have been summarized in a cent monograph (1951). Gelfand (1946) emphasized the fatty filtration of the liver and the intestinal atrophy, and drew attention the frequency with which there was a thick layer of subcutaneous t which, as Russell (1946) remarked, gave, with the oedema, a urious healthy-looking plumpness to the affected children. The t led Gelfand to doubt if malnutrition was an aetiological factor. he introduction of liver biopsy, the growing knowledge concerning etary liver injury in animals, and the recognition that fatty infiltra- on of the liver was not a terminal phenomenon, led to further tailed studies of the liver in kwashiorkor, summarized in Waterlow's 948a) monograph. Waterlow was chiefly concerned with the liver sions, but he drew attention to the marked atrophy of the pancreatic inar cells, previously recorded by Bablet and Normet (1937) t not regarded by them as an important lesion. Davies (1948a, 51) and Véghelyi (1950a) stressed the seriousness and importance the pancreatic damage, the severity of the degree of atrophy of e acinar cells, and the fact that pancreatic atrophy preceded the ty infiltration of the liver. Davies (1948a) suggested that children th kwashiorkor might be regarded as having virtually undergone pancreatectomy as regards the acinar tissue, and that the fatty er developed as a consequence of lack of pancreatic secretion. here have since been many reports of the histological changes in e pancreas (Hartz, 1949; Van Der Sar, 1951; Manson-Bahr, 50–51). Involvement of the salivary and lachrymal glands was o noted (Davies, 1951). Whatever name has been used for the nical condition and despite slight variations, especially in the skin ions, the pathological descriptions from all over the Tropics and ewhere have been in remarkable agreement. This suggests that oughout the Tropics the same factors are operating to produce ilar lesions.

The descriptions which follow of the pathology of kwashiorkor are sed on studies of material obtained in Kampala. The unanimity description in the literature makes it seem probable that the findings l apply elsewhere.

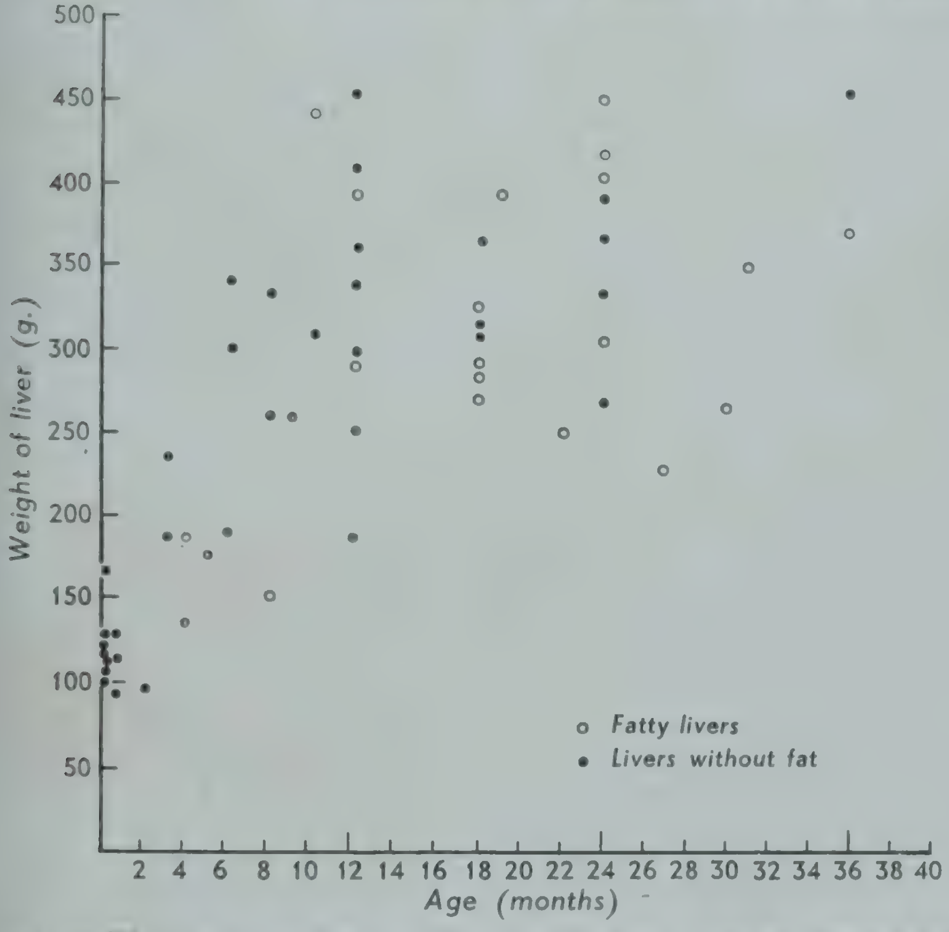
2. Gross appearance at autopsy

The lesions found at autopsy will vary with the severity of the condition, and the amount and duration of any treatment. In a severe case, the hair is coarse, straight, and of a brown, red, or even a flaxen to whitish colour. If the case has been treated the hair may be darker and less coarse near the roots. The skin is usually pale save in the areas of hyperpigmentation and the hyperpigmented patches can be easily rubbed off, leaving a weeping surface underneath. The areas which are thus denuded of epithelium, and the excoriated areas, particularly those in the fissures or on the hands, may closely resemble burns.

The general appearance is one of plumpness and pallor, the latter being specially marked around the mouth. The plumpness is due in part to the widespread watery oedema which is usually most marked in the legs but may be generalized: the face, thoracic skin, and the abdominal skin are usually more affected than the skin of the arms. To a considerable extent the skin and subcutaneous tissues bear the brunt of the oedema which is less obvious in the muscles. The other cause of the plumpness is the presence, in many cases, of a layer of subcutaneous fat, which may be a centimetre or more thick and is often more apparent in the upper arms and thighs than on the trunk. There is often a considerable amount of fat in the mesentery and omentum, in the retroperitoneal tissue and in the cheeks. This fat is generally highly coloured, sometimes a primrose yellow shade, somewhat reminiscent of the colour of the fat of an untreated case of Addisonian anaemia. In other cases there is more wasting than plumpness, oedema may be slight and only remnants of the panniculus adiposus are to be found, with scanty collections of fat elsewhere. Cases of this kind resemble the picture of marasmus seen in early infancy, but the degree of wasting is usually not so great, and there is a considerable amount of fat in the liver.

On cutting into the thigh and removing the swollen and turgid skin and subcutaneous fat, the wasting of the underlying muscular tissue becomes apparent. The muscles look pale and often have a greyish red tint. When the abdominal cavity is opened there may be a slight, or in some cases a considerable amount, of clear yellow fluid in the peritoneal cavity. The liver is seen to drop forward and to be of a bright yellow or tawny orange colour. It is usually not ich enlarged (Fig. 11) though the capsule is tense. After incision tissue bulges, and much fat can be seen on the surface of the ife. The liver is remarkably bloodless, and the cut surface ows a uniform yellow colouring with obscuration of the lobular rkings. In older children and in adults some degree of peri- ular fibrosis can be recognized.

The picture is often modified in the presence of severe anaemia malaria. In severe anaemia, where malaria is not present, the er may be a light buff or even stone colour. When the child been suffering from malaria the intense malarial pigmentation y cause the liver to be a light purple in colour, the usual slate- y pigmentation of malaria being diluted by the amount of fat sent. In such cases the lobular outline is often picked out by a k ring of pigment. In uncomplicated cases of kwashiorkor the -bladder is usually full of light yellow-green watery bile.



IG. 11.—Weight of the liver in Uganda African children at various ages. The weight of fatty livers (shown by circles) was not consistently different n that of livers that were not fatty.

The pancreas is usually pale in colour, sometimes almost dead white, and is often grossly atrophic, being shrunken to a small cord of tissue stretching from the duodenum to the spleen. It is usually rather firm and in older children may be very firm and rigid. It keeps its shape well and there is no evidence of interlobular fat replacement. The intestines, particularly the small intestine, are very atrophic, the walls thin and diaphanous so that print can sometimes be read through them. They may be distended with gas and masses of undigested food may be present. There may be an excessive amount of mucus, not only in the intestine but also in the stomach, and it is not unusual to find excessive amounts of mucus and gastric contents in the oro-nasopharynx. The stomach wall is never so much thinned as the wall of the small intestine. The large intestine is often normal in appearance, unless there has been some terminal dysenteric complication. The mesenteric lymph glands are often enlarged and pinkish-white in colour, and have a firm consistency.

Examination of the thorax shows the thymus to be very atrophic, so atrophic in some cases that it may be hard to find any remnants (Vint, 1936–37). There is often evidence of mild infection of the trachea and bronchi. Bacterial infection of the lung, usually broncho-pneumonic in type, is very commonly seen, and even if not infected, the lungs are generally heavy with oedema. There may be small exudates in the serous cavities. The heart usually shows no change save for a pallor of the myocardium, especially marked in the inner portions of the ventricular walls. The thyroid may appear rather pale.

The kidneys are often pale with a peculiar light-greenish pink tint of the cortex. The cut surface bulges and fatty streaking of the medulla is sometimes seen. The parotid and the other salivary glands do not commonly show any abnormal appearances though they may be paler than normal. The lachrymal glands too may be pale and are often small and rather difficult to find. The brain and the pituitary usually show no naked-eye abnormalities, but there may be some degree of oedema of the brain. The bones usually look normal, but there is sometimes a swelling of the costal cartilages which has in life been mistakenly diagnosed as a rickety rosary.

Most cases of kwashiorkor in childhood which come to autopsy in Uganda have died in the florid stage with oedema, and with a good deal of fat in the depots. Occasionally, however, a case is seen which is passing, or has passed, from the oedematous stage to one of marasmus. Even here, however, there are differences from the typical marasmic picture : in the experience of the writer (J. N. P. D.) there has never been any difficulty in distinction, for the extreme emaciation and lack of fat typical of marasmus is not seen in kwashiorkor save in the most severe cases in which death has been due to gastro-enteritis.

The pathology of kwashiorkor is often modified by the presence of severe bacterial infections. In some of these infected children, who exhibit the changes in the skin and hair, and are oedematous, there may be little evidence of fat in the liver and the atrophy of the pancreas and intestine may appear minimal. In older children too, and in those who have been suffering from kwashiorkor for some time, the fat in the liver may be minimal but the pancreatic atrophy is always marked.

In children who have died after receiving a high-protein diet for some time the appearance of the liver and pancreas may be considerably altered. The differences are most marked in the pancreas, which becomes swollen and slightly congested and is no longer white in colour. The difference may be seen, to a lesser extent, in those who have been on the ordinary hospital diet for a few days. A very slight improvement in the diet, particularly in the protein content, may make a considerable alteration to the appearance of the pancreas, which changes from a picture of severe atrophy to one of partial recovery. This may in part explain why attention was drawn to the pancreas rather late in the history of the disease, and why some reports of typical cases of kwashiorkor state that the pancreas was examined and found to be normal (Walt, Wills and Nightingale, 1950). If cases of untreated kwashiorkor are examined the characteristic atrophy of the pancreas is always visible. The changes in the liver following protein feeding develop more slowly, but even a few days of hospital food may produce some alterations, especially in the vascularity of the liver. It soon becomes apparent hat more blood is present in the liver and that the consistency has ltered.

. The histopathology of kwashiorkor

A thorough and systematic study of all the organs and tissues f the body in cases of kwashiorkor has not yet been made. Attenion has been paid chiefly to those organs in which there seems to e obvious damage, which seem to be the most severely and speedily involved, and whose malfunctioning seems to be of importance in aggravating the deleterious effects of the poor diet which is believed to be the chief cause of the disease. Prominent among such organs is the liver. The introduction of liver biopsy and the work of Gillman and Gillman (1945b) drew attention to the real significance of long-continued fatty infiltration of the liver in kwashiorkor at a time when a great deal of work by many investigators was focusing interest on the consequence of prolonged fatty infiltration of the liver in animals.

(*a*) The liver in kwashiorkor

Views upon the microscopic anatomy of the normal liver have undergone some marked changes during recent years, largely due to the work of Elias (1949a, b, 1953). Though there still remain a number of unsolved problems, particularly those relating to the blood supply of the liver lobule (Andrews, Maegraith and Wenyon, 1949; Maegraith, 1951), and our views may yet be modified, it would appear that Elias's work has given a much truer picture of the anatomy of the lobule than obtained before. In the discussion that follows it will be clear that Elias's views are in general accepted.

(*i*) *Fat in the liver.* The gross appearance of the liver in a severe florid case of kwashiorkor suggests the presence of an amount of fat which is always considerable and may be extreme. In the later years of childhood, however, a child with a similar clinical picture may have no demonstrable fat in the liver (Davies, 1948a). Similarly in the very early cases there may be little fat present even though there is histological evidence of pancreatic atrophy. Under treatment, as already mentioned, the fat slowly disappears. What occurs in untreated cases, if they survive, is a matter for speculation, but probably the fat disappears very slowly. Whenever there is only a little fat present in the livers of uncomplicated cases of kwashiorkor, it is always in the same place; that is, in the peripheral cells of the liver lobule (Fig. 12, and see Davies, 1951). The cells of the lamina limitans of the portal triad do not usually contain fat in the early stages (Fig. 13 (*a*)). The fat appears first in small droplets which coalesce till the cells become full of fat while the nuclei are pushed to the side. As the fat accumulates in larger droplets in the peripheral cells, there is an increasing amount of fat appearing in the cells situated lower down the liver cell plates and towards the central vein. Last of all the cells near the central vein become full of fat and the liver may be so fatty as to resemble a section of adipose tissue. The severe cases of kwashiorkor show practically every cell in the liver lobule to contain a large droplet of fat, so that only a small amount of cell cytoplasm is visible, although even then, some of the lamina limitans cells may not contain much fat.

The initial deposition of fat in kwashiorkor (in the absence of severe bacterial infections) always follows this pattern, the fat being

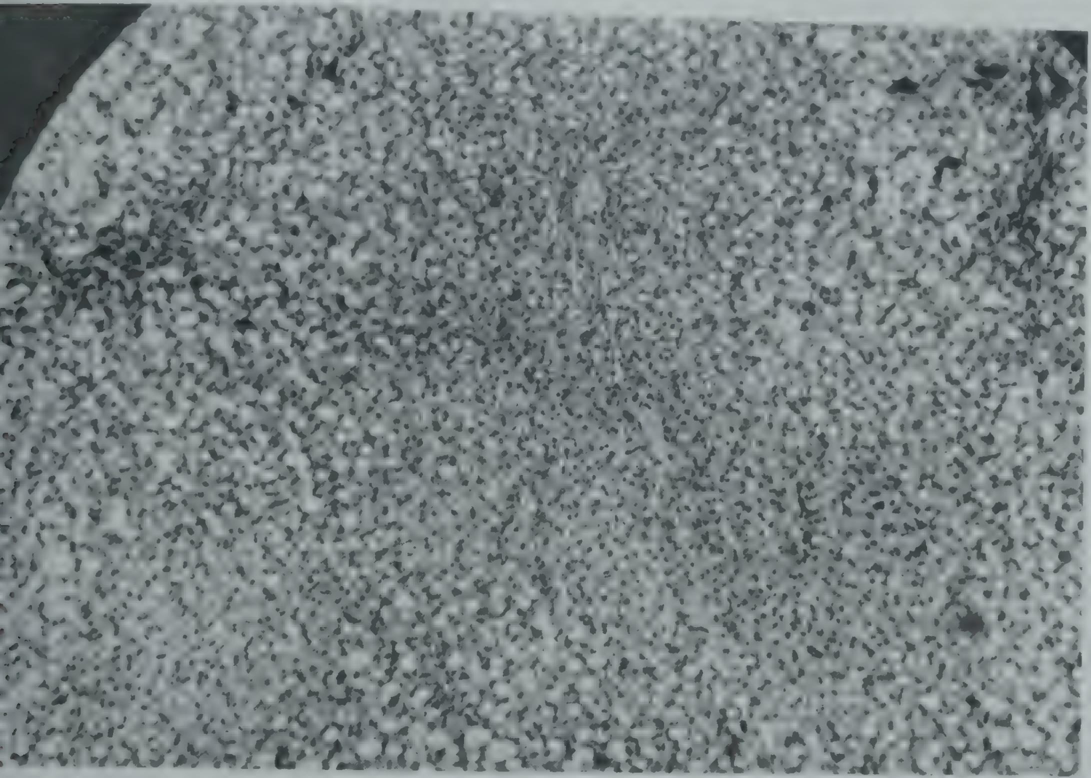


FIG. 12.—Liver. Early stage of fat infiltration in kwashiorkor. Boy, 1 year old.

The fat is mostly in the peripheral areas of the liver lobules with relative sparing of the liver cells round the central veins. There is a tendency for the liver lobules o be outlined by malarial pigment.

Stained with haematoxylin and eosin. Magnification × 75.

deposited first in the periphery of the liver lobule followed by progressive involvement of cells towards the central vein. It has een claimed that to show the exact location of the initial fat deposi-ion in the liver lobule, and even the distinction between the portal nd hepatic veins, injected preparations must be studied. How-ver true this may be in experimental animals, and in human livers vhere the architecture is grossly distorted by fibrosis, injection hould not be necessary in the livers of children only moderately ffected by fatty infiltration or by fibrosis. All studies of the liver n kwashiorkor since the first reports of Gillman and Gillman

(1945b) have emphasized that the fat is deposited first in the peripheral liver cells, and injection studies in Uganda have confirmed this. The identification of the locus of the early deposition of fat (Fig. 13 (*b*)) was made an easy matter by the fact, fortunate in this respect, that so many of the Uganda patients were suffering, or had suffered, from malaria. After an attack of malaria many sinusoidal cells, and the Kupffer's cells, contain dark malarial pigment (Taliaferro and Mulligan, 1937). It slowly leaves the cells and passes more and more peripherally till ultimately it collects in masses towards the edge of the liver lobule, and in the portal triads (Dudgeon and Clark, 1917; Maegraith, 1948). The periphery of the liver lobule is usually sharply outlined by the pigment accumulations. The liver has injected itself, and visitors to the Tropics, who are unfamiliar

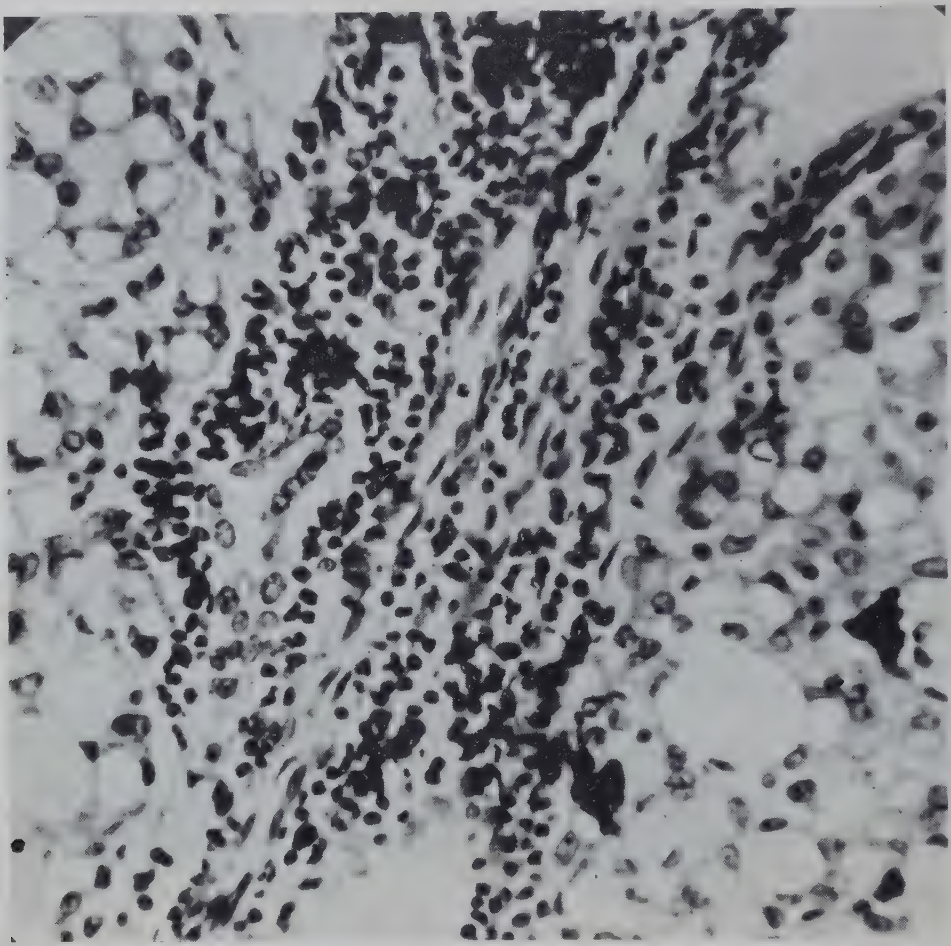


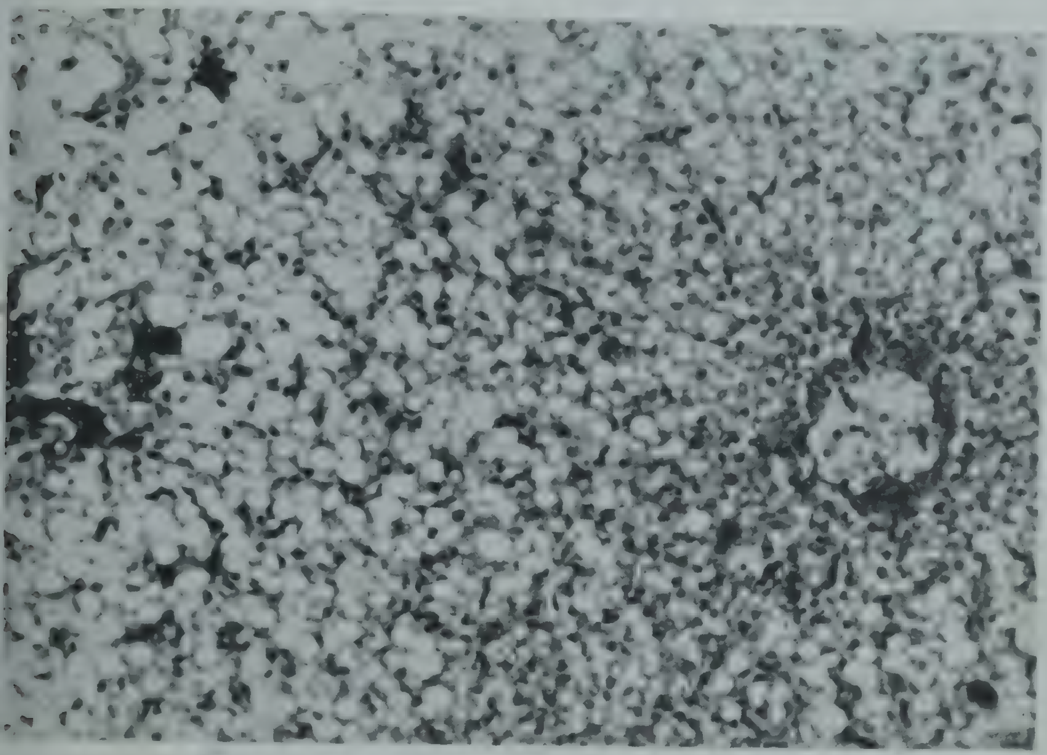
FIG. 13 (*a*).—Same liver as Fig. 12. High-power view of a portal triad showing cellular infiltration and some large spaces, possibly representing the fusion of several fat-laden cells.

Much malarial pigment is present, in large and small masses. Some of the liver cells contain no fat, but others are grossly distended with it.

Stained with haematoxylin and eosin. Magnification × 250.

with this phenomenon, have been known to congratulate investigators on the skill and neatness of the injection. The pigment accumulation is an unexpected advantage to the pathologist working in the malarious Tropics. Alas that it is so rarely seen in adults with cirrhosis.

But where kwashiorkor is complicated by some serious infective process, particularly tuberculosis, the initial deposition of fat is not



IG. 13 (*b*).—Same liver as Fig. 12. Showing fat infiltration of the liver lobule at a moderately early stage.

Portal vein area to the left with considerable amounts of dark malarial pigment. entral vein to the right and one pigment mass. The larger fat globules are away om the central vein in the periportal areas.

Stained with haematoxylin and eosin. Magnification × 120.

ıvariably peripheral (Davies, 1948a). It is often quite irregular, arying from lobule to lobule, being central, mid-zonal, or peripheral in different lobules, and there may be much more fat in one bule than in its neighbours, in contrast to the uniform pattern een in cases not so complicated. The phenomenon has been equently observed in Uganda and was also noted by Véghelyi 950a) in his studies of malnourished children in Budapest. When suspected kwashiorkor histological studies of the livers of children veal centro-lobular fat infiltration, the cases are not typical and ncomplicated, but are early stage cases complicated by a severe infection. Observation of centro-lobular or of irregular fat deposition in a biopsy specimen has on several occasions directed th attention of clinicians to a hitherto unsuspected infective element

When fat disappears from the liver it leaves in the reverse orde from its coming, disappearing first from the centro-lobular region anc

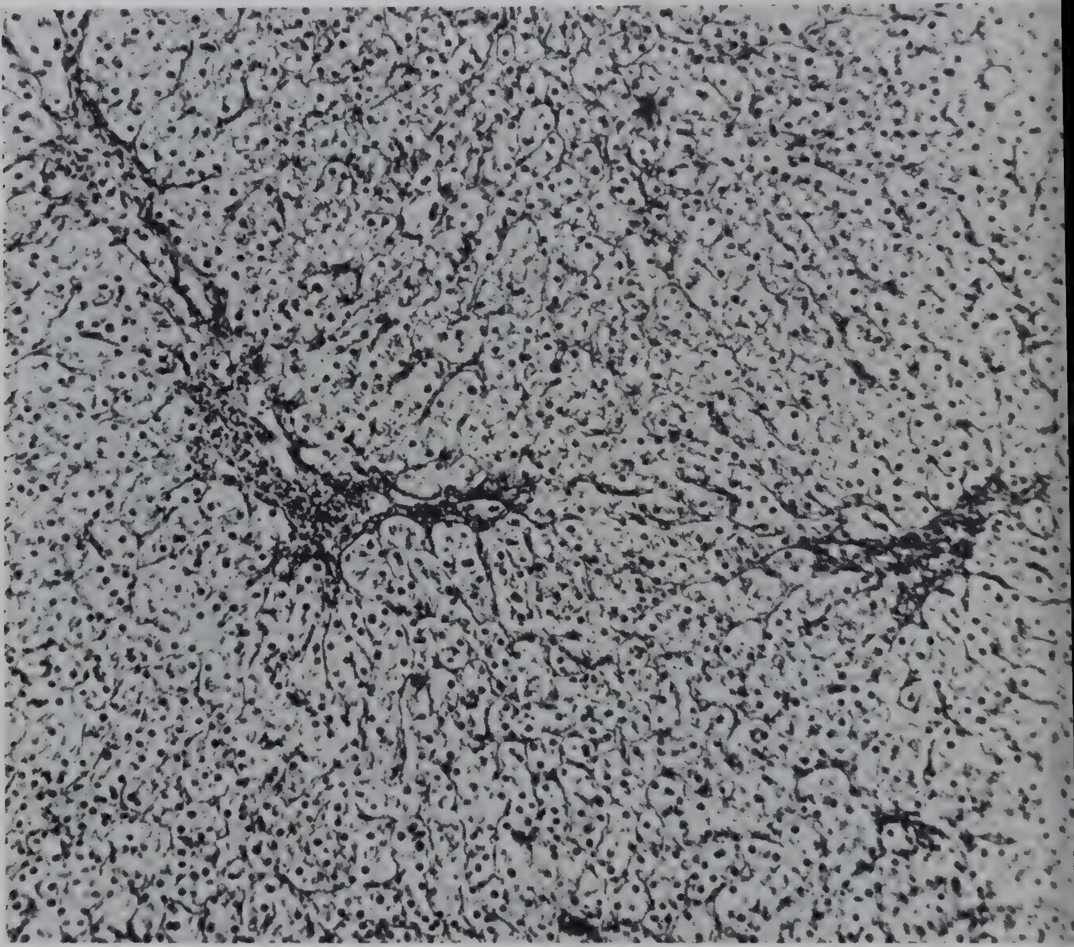


FIG. 13 (*c*).—Liver. Late kwashiorkor.

Biopsy from boy aged 5 years, showing reticulin thickening at the periphery of the liver lobule tending to form a scarred, star-shaped area in the portal triads with extensions outwards to delimit the liver lobules.

Silver stain for reticulin. Magnification × 75.

last of all from the periphery. The fat droplets diminish in size, break up into smaller droplets and then disappear. As the fat leaves the cells a watery glycogenic vacuolation becomes visible, producing a foamy appearance. If treatment continues this disappears, the cells "firm up" and become normal in appearance. The same watery vacuolation is often marked in the cells where the fat deposition is occurring, the large vacuolated cells resembling those described as hypocytoplasmic liver cells of protein deficiency (Elman and fetz, 1941; Kosterlitz, 1947).

The disappearance of fat from the liver is a slow and uncertain erion of improvement, and it may be several weeks, even in l-treated cases, before the fat leaves the cells in the periphery of lobule.

When the fatty infiltration of the liver is maximal and all the s are distended with fat it is not unusual to see cells whose tched walls have disappeared with coalescence of the fat from or more cells to form a larger globule (see Fig. 13 (*a*)). This is er a very marked feature and only affects a few cells. In animals in adults with severe fatty infiltration it is more apparent, and troft (1950, 1951) has paid particular attention to these so-called tty cysts" in experimental animals. From his studies it would ear that the cysts are very important lesions in animals and in lt humans who suffer from prolonged fatty infiltration of the liver, t is often near them that fibrosis starts (Hartroft, 1950, 1951). reover, the fat in the cysts is not easily mobilized through the uence of lipotrophic agents. The fat may rupture into the phatics or the bile capillaries, in which case it does little harm, hrough the sinusoids into the blood-stream, in which case it may l to showers of minute fat emboli which may cause lesions in er organs. The fate of the cysts in kwashiorkor awaits explora- n. Though coalescence of fat droplets in the liver has been erved, it is always on a small scale and no fatty cysts have been erved in cases in Uganda persisting after the disappearance of from the liver cells. This does not, however, preclude the sibility that during the maximal degree of fatty infiltration of liver small fat emboli may find their way into the blood-stream damage other organs. Such happenings might explain some he clinical features of kwashiorkor, possibly even some of the ntal changes.

ii) *Cellular accumulations in the liver.* Cellular infiltrates in the al triads accompany the infiltration of fat into the liver in children kwashiorkor (Fig. 13 (*a*)). They appear first in the portal spaces cent to a collection of blood-vessels or a bile-duct, or in the angles ne portal triads. The earliest cells to arrive are the lymphocytes mpanied, particularly if there is a hookworm infection, by ophil cells. In some cases macrophages and neutrophil poly- phonuclear cells may be present in appreciable numbers, but

the majority of the cells are mononuclear cells, most of them lyr
phocytes. They are not confined to the portal triads, but are oft
in considerable numbers in the sinusoids, with a predeliction
accumulate at the periphery and to avoid the region of the centr
vein. Serial biopsies suggest that they move about in response
the mobilization or deposition of fat. When the liver is gross
fatty the portal triads are often packed with cells, but there are fe
in the sinusoids. When treatment leads to the rapid mobilizati
of fat from the liver the sinusoids become flooded with lymphocyt
(neither these nor the macrophages have been seen to contain fa
and there appear to be fewer cells in the portal triads (Davies, 195
In older children suffering from kwashiorkor in whom there is litt
or no fat in the liver there are few lymphocytes in the sinusoids, b
a considerable number in the portal triads. This relationsh
between the localization of the lymphocytes in the liver and t
movement of fat into and out of the hepatic cells suggests that the
may be some functional association, although there is no eviden
concerning what this might be. The lymphocytes, as sever
investigators have shown, possess lipolytic enzymes whose physi
logical functions have never been determined (Bergel, 191
Fiessinger, 1923; Barnes, 1940). Neither a lymphopenia in t
blood, nor a lymphocytosis, has been noted during these stages
the removal of fat from the liver.

Little attention has been paid to the appearance of the liver
the African child during the early months of life, but such studi
as have been carried out in Uganda have not shown accumulatio
of cells in the portal triads to be at all frequent before the onset
kwashiorkor and the deposition of fat in the liver. Both fat ar
cells appear about the same time so that there seems to be a conne
tion between the two. The cells are present, however, in the port
triads long after all visible fat has disappeared from the liver, ar
indeed it is rare to see a liver from an adult African that does n
show considerable collections of cells in the triads (Vint, 1930–31
Gillman and Gillman, 1945): far more are seen than in the live
of Europeans, in whom it is not uncommon to see a certain increase
cellularity in the portal tracts. Why, in view of the short life spa
of such cells, there should be this continuing cellularity of the port
triads is a mystery, but it does suggest that there is some sort
persisting damage to the portal tracts if not to the actual liver cell
which often appear hypocytoplasmic. The cellular accumulation

y be related to damage to the intestinal wall or to the passage of oxins" from the intestines, but they are not more marked when re are obvious lesions in the alimentary tract. The accumulations m in part to reflect the white cell count in the circulating blood, a septicaemia causes numbers of neutrophil polymorphonuclear ls (but not lymphocytes) to reinforce the lymphocytes and other nonuclear cells in the portal spaces.

Amongst the cells in the portal spaces there are observed many nma-shaped, elongated or spindle-shaped darkly-staining nuclei. terlow (1948a) has suggested that they are the nuclei of fibrocytes l that their appearance accompanies the development of a fine iportal fibrosis. They only appear after there has been fatty ltration of the liver for some time. The cells present in the tal triads are therefore of a very varied nature and unless biopsy dies are made the sequence of events is not easy to determine, in the later stages there may be a great mixture. Few of the s seem to be connected in any way with the presence or absence nalarial pigment in the liver, whether that is inside cells or is in form of free masses in the portal triads. Nor is there evidence ologically of any unwonted activity of the Kupffer cells.

(*iii*) *Fibrosis in the liver*. The observations of Elias (1949a, b, 3) support the view that the portal triads in humans are sharply mited from the liver lobules, firstly by the tenuous delicate ous sheathing of the portal triad canal, and secondly by a rounding sleeve of liver cells, the lamina limitans. Both these ings are penetrated here and there by vascular, lymph and bile nnels, all of which connect the lobule with the portal canals. A ly in Uganda of the livers of African still-births, neonates and nts has not shown any evidence to suggest that the African liver nfancy is different in its anatomical structure from the livers hildren of other races (Potter, 1952). Silvera and Jelliffe (1952) Edington (1952 *Proc.*) have suggested that in the livers of many ng African infants, and even in the foetus, there may be quite rmal amounts of fat present, and that this is most commonly d in the centro-lobular regions. Apart from these observations is no evidence that the African liver in infancy is abnormal and the concepts of Elias do not apply. An unusual pattern of the us tissue in the liver of an African child therefore represents an rmality, whatever its aetiology or its significance.

he first significant changes that are seen in children with kwashiorkor are in the reticulin fibres which form a lattice framewo round the individual liver cells, thinner in the central regions a thicker in the periphery of the lobule. In the early stages of t periportal fat infiltration the reticulin fibres round the peripher cells, including those of the lamina limitans cells which may exhi no fatty changes, swell and thicken and they may either split, further fibres may condense out of the medium, so that the ce become surrounded first by a double strand of reticulin and late as they continue to reduplicate, by an increasing number of newl formed fibres (Waterlow, 1948a; Davies, 1948a). While th process is most marked in the neighbourhood of the portal triads occurs in a regular fashion round the limits of the liver lobule (The process has been illustrated by Waterlow, 1948a.) The per pheral cells degenerate and disappear and the fibres thicken a condense round the collapsing cell and begin to take the stains f collagen. Finally the effect is to delimit the lobule so that the ou line of the lobule becomes apparent (Fig. 13 (*c*)); the outlining i to a greater or lesser extent, a feature of almost all livers in Afric adults. The initial thickening of the reticulin fibres is along th sinusoids. Subsequently thickening occurs of the fibres between th individual cells and, while there is strangulation of the peripher cells, there is an extension of the process down the sinusoid Collagenization is most marked in the portal triads and the fibros spreading out from these regions in a radiating pattern with the mai extensions along the periphery of the lobule. As collagenizatio continues, a star-like pattern of fibrosis, " stellate fibrosis ", develop at every portal triad with a disturbance of the normal architectur

The rate at which thickening of the reticulin fibres and collagenization develop in the liver of children with kwashiorkor does not see to depend either on the rate or the intensity of the fatty infiltratio or on its severity, or on the prolongation of the period of infiltratio In fact there may be considerable fatty infiltration in the liver fo many weeks before any degree of collagenization is noted.

In the early stages the sequence of events described the change at the periphery of the lobules might well be called an " intercellular cirrhosis " (Rolleston and McNee, 1929). But as the delimitation of the hepatic lobule, and the continuous increase in th fibrous tissue radiating from the portal triads, become more obvious it is clear that what is developing is a monolobular or annular typ of " cirrhosis " in which a ring of fibrous tissue is tending t rround each and every lobule. This is not, however, a “ biliary rhosis ”, but only resembles that condition in that the outline of h lobule becomes clearly marked (Saphir, 1929 ; Mallory, 1948). e process can be arrested at any stage, but the arrest depends on tors which are obscure. Four possibilities present themselves. stly, restoration and reversion to normality—but this appears to ppen very rarely, if at all, according to experience in Uganda. condly, the process may be arrested with only minimal thickening the reticulin framework : this again would seem to be unusual. irdly, and most frequently, the process continues till there is well- rked stellate fibrosis in the portal triads with reticulin thickening ng the periphery of the lobule. Fourthly, in a few cases the ocess continues till strands of collagenous tissue surround all the r lobules—a condition which is rarely seen in children in Uganda is more common in adults. Long ago, Vint (1930–31) in Kenya w attention to the frequency with which such a monolobular or ular type of cirrhosis was seen at the autopsy of adult Africans. 100 consecutive autopsies he found the process so developed that 63 he considered that it could fairly be described as “ cirrhosis ”. nor degrees of the fibrosis, corresponding to what the writer fers to call a “ stellate fibrosis ”, were found in all Vint's cases. t's experience corresponds with the general experience in Uganda, ere, save in very young children, it is rare to find a liver from an ican patient which does not show, to a greater or lesser extent, ellate fibrosis radiating from the portal triads, with an accompany- cellular infiltration. With advancing age these changes seem to ome more marked. Similar observations as to the frequency of r scarring, sometimes, but not always, accompanied by deposition ron, have been reported from Johannesburg (Gillman and Gill- , 1948b), while the writer has seen scarring without iron deposi- in livers in the Sudan and in West Africa.

The origin, persistence, and indeed the accentuation of the stellate osis, and the persistence of the cellular accumulations, are resting and puzzling phenomena. It is well recognized that a iderable amount of fibrosis may develop in the liver, but sub- ently regress to leave a histologically normal liver. This was demonstrated by Cameron and Karunaratne (1936) in their es of the development of cirrhosis in the rat liver after the nistration of carbon tetrachloride. Their observations have confirmed in other animals after fibrosis has been induced by a variety of means, and it has been stated that a similar regression of fibrosis can take place in human livers. Yet in Uganda an elsewhere the stellate fibrosis and the cellular infiltrations seem t persist indefinitely from their first appearance in the weanling chil Moreover, Mall (1906) showed that the liver structure in childhoo is entirely rearranged each year with particularly rapid changes abou the time of puberty. The retreat of fat from the liver in kwashiorko does not leave behind an architecturally normal liver, and the injur would appear to reach an irreversible stage within a few weeks c the onset of kwashiorkor. The continuing process may be associate with the not infrequent finding in the peripheral regions of fat-fre African livers of the " dark cells" of Clara (Clara, 1931; Pfuh 1932; Cameron, 1950).

It has been suggested that fibrosis in the liver can only regres provided that there is no interference with the vascular supply c the liver lobule by the fibrous tissue. The persistence of the stellat fibrosis may therefore be due to its developing in areas where i can hardly fail, if appreciable in amount, to affect the blood suppl to the liver lobule—a factor which may lead to its increase by process of self-aggravation. Thus in the livers of older childre and adults the fibrosis is more apparent, even in the absence of fatt infiltration, and in cases in which there is no reason to suppose tha fat has been present recently. It is of course possible that " toxins ' from the gut may play some part in the continuance and accentuation of the fibrosis. This is hypothetical: but on the other han it is certain that the child or the adult usually continues to eat a die low in protein and associated factors, and that the resulting depletion of the hepatic cells may favour a continuation of the sam pathological patterns.

The stellate fibrosis, the thickened reticulum and the cellula infiltrations may provide an anatomical substrate for the recrudescence of a fatty infiltration and progressive sclerotic changes should the subject again pass through an episode of severe malnutrition. This conception was put forward in the case of pellagrou skin lesions by Denton (1925), who showed that, following an attac of pellagra, full reconstitution of the skin did not take place, but permanent defect remained which favoured an eruption in the sam region should a pellagrous state again occur. Thus the well-know adage " once a pellagrin, always a pellagrin " has part of its background in a residual defect. It is almost as true to say " once ashiorkor, always a kwashiorkor " in that later in the life of a ashiorkor patient a further period of malnutrition or an infection, rticularly tuberculosis, may precipitate a further attack with some the same clinical signs, such as oedema and dyspigmented hair, d some of the same pathological changes in the internal organs . 249).

The stellate fibrosis is moreover so frequent in Africans that it is confusing factor when some further injurious process affects the er ; such injuries—infective hepatitis, acute liver necrosis, histosomiasis, arsenical and other poisonings—are very frequent African life. All these, and other processes, can only add their rticular seal to a liver already scarred and stamped, so that the al picture is most involved and difficult to interpret. It is with ict justice that Cullinan (1945–46) stigmatized the African liver a " histological nightmare ".

(*iv*) *Pigmentation of the liver.* The frequent presence of malarial gment in the livers of children with kwashiorkor who live in alarious areas has been noted. It seems to be quite innocuous, to cite no reaction, and to disappear ultimately without leaving any ces of its passing. It is not commonly seen in the livers of older ildren or adults unless there has been a recent clinical attack of alaria. The non-immune immigrant, recently arrived in a highly alarious area, may show it well. It is the only pigment present any extent in the livers of children or adults studied in Uganda, d in other areas of East and West Africa. In South Africa illman and Gillman, 1948b, 1951) and in the Gold Coast (Edington, 52 *Proc.*) attention has been drawn to the great frequency with ich considerable amounts of iron are seen in the livers of Africans. ey are rarely seen in children under the age of 6 years, but tend increase with advancing years. About 10 per cent of adult icans studied in Johannesburg are said to have cirrhotic livers ntaining considerable amounts of iron. There is thus a difference ween the findings in South Africa and the Gold Coast and those other parts of Africa. The frequency of iron pigmentation of liver would appear not to be, as has been strongly maintained Gillman and Gillman (1951), a direct consequence of malnutrition, to follow a gross excess of iron in the diet (Walker, 1951 ; ginson, Gerritsen and Walker, 1953). The iron cooking pots in ch the food is prepared are said to be the chief source of the iron, so high is the iron content that much will pass the normal mucosa, and be deposited in the liver and other organs. It may be that the process is aided by a deficient diet, as suggested by the results of animal experiments (Kinney, Hegsted and Finch, 1949 ; Hegsted, Finch and Kinney, 1949), and a dietary deficiency may be a major factor.

It is perhaps necessary to stress these findings, and particularly the fact that considerable accumulations of iron are not usually seen in the liver of young African children, because certain misconceptions have arisen. It must be emphasized that iron is not found in great excess in the livers of weanling children with kwashiorkor anywhere in Africa. In fact, save for malarial pigment, there are no notable pigmentary changes in the livers of most children with kwashiorkor.

(*v*) *Necrosis of liver cells.* Mention has previously been made of the breakdown of cells grossly distended with fat to form fatty cysts. This is not a very notable feature of the livers of kwashiorkor cases in Uganda. The presence of occasional " dark cells " and the engulfing and apparent strangulation of some of the cells at the periphery of the lobule by thickened reticulin fibres has also been noted. Apart from these changes, necrosis and death of liver cells has not been a feature of the livers studied in Uganda by biopsy or at autopsy. Massive liver necrosis and infective hepatitis are not common in African children though necrosis is sometimes seen following the exhibition of hepatotoxic anthelminthic drugs, and focal or centro-lobular degenerative changes are frequently seen in acute infections, both in children and adults. However, there is some evidence that piecemeal necrosis may be going on in the livers of African children and adults, even in the absence of recognized infections and toxic processes. Attention has been drawn (J. Gillman, 1940) to the greater frequency of binucleate and multinucleate cells in the livers of Africans, and mitotic division, rarely seen in the livers of Europeans (Cameron, 1950), is not uncommon in African livers (Bergeret and Roulet, 1947). The significance of these observations and their relationship to the development of fibrosis is not yet understood.

(*vi*) *Fibrogenesis in the liver in children in the Tropics.* Before proceeding to a description of the pathological changes in other organs, further consideration will be given to the fibrogenetic processes at work in the livers of children with kwashiorkor. Care has been taken to avoid any suggestion that the fibrosis that develops n the liver in kwashiorkor is due to the fatty infiltration. In fact, hough these lesions appear superficially to go together, in actual act they develop separately and to some extent quite independently. Their relationship is obscure. Neither the amount of fibrosis nor he rate of its development appear to depend on the extent or uration of the fatty liver infiltration. An extreme degree of atty infiltration may persist for a long time with but a minimal egree of fibrosis. On the other hand, a marked fibrous reaction ay develop where there appears to have been no more than a oderate amount of fatty infiltration, and this only over a short me. Caution in the interpretation of the linkage between the evelopment of the fibrous and the fatty infiltration is the more ecessary because in the Tropics there appear to be several types of brosis of the liver which develop without fatty infiltration.

The best known is the infantile cirrhosis which is found in ertain Indian children. It is seen *as a marked cirrhosis* in children etween the ages of 3 months to 3 years, mostly among upper-class eople who live on a strict vegetarian diet. Children present with undice and enlarged livers with evidence of portal vein obstruction, nd die of cholaemia if not of some intercurrent infection. Several ildren of a family may be affected. Few autopsies have been corded, but Radhakrishna Rao (1935–36, 1936–37) published a etailed study of the liver lesions. The necrosis of the liver cells, hich is a marked feature of the disease, seems to be the result of an terference with the free flow of blood from the tributaries of the rtal vein, because of an endophlebitis, phlebosclerosis or partial rosis of the hepatic venous vessels. The result of this cellular generation is a collagenization of the reticular framework of the rresponding sinusoidal bed. The result is “ an avascular, non-flammatory oedematous connective tissue network ”, enclosing in meshes small sized islands of hepatic parenchyma of very unequal es and in varying degrees of degeneration. Signs of inflammation usually lacking, but sometimes there is evidence of a widespread olangitis. There is often evidence of considerable bile retention. o concluded that this disease should be termed “ a subacute ic cirrhosis ”. The disease, although interesting, probably bears relation to kwashiorkor and obviously presents a most unusual striking series of pathological changes which are not seen nmonly elsewhere in the Tropics.

Another type of hepatic fibrosis has been described from the

West Indies, and its pathogenesis in part elucidated (Hill, 1951; Hill, Rhodes, Stafford and Aub, 1951, 1953; Rhodes, 1952). Here again the picture of fully-fledged cirrhosis is seen even in young children. The disease, which has been called "collagenosis of the liver", or "serous hepatosis", is not hereditary or familial. The children have lived on poor diets largely composed of carbohydrates and deficient in protein, fats, fresh fruits and vegetables. In the acute or sub-acute stage the children are stunted but appear well nourished with sturdy legs and normally developed muscles; the liver, however, is firm and enlarged and is sometimes tender. Ascites eventually occurs but generalized oedema is not seen. The children will eat readily any protein foods but dislike carbohydrates. In the later stages there is wasting with gross ascites and hepatosplenomegaly. The changes appear to follow a certain sequence of events occurring in the spaces of Disse and Mall. The initial lesion is a serous exudate in the spaces round the sinusoids and the centro-lobular vein, the liver cells being compressed but otherwise healthy. The exudate changes to an eosinophilic coagulum which undergoes fibrosis. The final picture is that of a massive hepatic fibrosis with lobular distortion, reactive bile duct proliferation, and nodular regeneration. The sequence of events bears a resemblance to that described by Rössle (1932, 1933), in the condition termed by him "serous hepatitis".

It is of great interest that among the cases studied by Hill and his associates were some of typical kwashiorkor, similar to those described by Waterlow (1948a) from the same area. In these cases severe fatty infiltration of the liver was noted and in the majority it was accompanied by the changes of serous hepatosis. This condition of "collagenosis" or "serous hepatosis" in West Indian children appears to have a distinctive liver pathology which differs fundamentally from the changes seen in kwashiorkor. The changes described in "serous hepatosis" have not so far been recorded from Africa, and in Kampala the lesions have not been noticed in any case of kwashiorkor. They cannot, therefore, be responsible for the fibrosis of the liver seen in Uganda.

Walters and Waterlow (to be published) have studied the development of fibrosis in the livers of young children in the Gambia who were suffering from severe malarious infestation. Few autopsies could be performed but a large series of liver biopsies was studied. The children did not present any of the more typical atures of kwashiorkor and their clinical condition appeared to be ore akin to marasmus (Brock and Autret, 1952). They were on e whole of a younger age group or at least the process was active om an early age. They exhibited growth retardation and hepatoplenomegaly ; the latter was possibly due to malaria, as the children the same area who were protected from malaria did not show it McGregor, 1952 *Proc.*).

In the Gambia the transmission of malaria is seasonal, and is at minimum in the dry season. Liver biopsy did not explain the epatomegaly but revealed that a fibrogenetic process was going on –reticulin thickening and collagenization in the periphery of the bule with strangulation of the peripheral cells, particularly near e portal triads, and with early delimitation of the lobular boundary. hough cases of kwashiorkor with severe fatty infiltration do occur the Gambia, these cases of hepatomegaly showed little or no fat the liver even when fibrogenesis was active. It is possible that e children may have had an episode of fatty infiltration previously Silvera and Jelliffe, 1952), but this seems unlikely and could only ave been brief. Unfortunately it is not possible to say if there ere notable lesions in other organs.

These interesting observations reinforce the view that it is not e presence of fat in the liver which is responsible for the fibrosis. n the Gambian children a stellate fibrosis develops which seems be precisely the same as that which develops in children with washiorkor, yet it probably develops without any considerable egree of fatty infiltration. Taking a wide view, it seems that two ifferent sets of aetiological factors are capable of operating, one ading to fatty infiltration, the other to fibrosis. In Uganda they ppear to be operating together, in the Gambia only the fibroenetic factors operate. It may be that in other areas only the ctors producing the fatty infiltration operate, for Hartz (1949) nd Van Der Sar (1951) pointed out that fatty liver disease in hildren in Curaçao does not lead to cirrhosis in later life. Corcos nd Tabbane (1953), writing from Tunis, say that fibrosis does not cessarily lead to cirrhosis.

All observations point to the vulnerability of the cells at the riphery of the liver lobule, for it is in these cells that the initial deposition takes place. They are affected the most severely and er the longest period, and are in the region where the collagenizan takes place. There is thus a considerable divergence between the findings in children with severe fatty infiltration of the liver and in experimental animals. In animals, diets deficient in lipotrophic factors lead to fatty infiltration in the centro-lobular regions and, as was first emphasized by Ashburn, Endicott, Daft and Lillie (1947), fibrosis starts to develop in the near central regions. It is now thought that it often starts adjacent to the fatty cysts described by Hartroft. On the other hand, in starvation fat may be seen in the peripheral cells of the lobule (Best, 1950).

The precise factors which lead to fatty liver infiltration in kwashiorkor await elucidation and so do the causes of fibrogenesis in the livers of African children. Until more knowledge is available profitable discussion is limited, but it may be worth while to direct attention to the possibility that the essential factor in the development of fibrosis may well be a persisting mild degenerative, hypocytoplasmic, necrotizing process in the peripheral cells with collapse and thickening and collagenization of reticulin fibres (Fernando, Medonza and Rajasuriya, 1948; Gyorgy and Goldblatt, 1949). The process may proceed in the absence of fatty liver infiltration. The factors responsible must be chronic and mild.

(*b*) The exocrine enzyme secreting glands

(*i*) *The pancreas.* The finding that the fatty liver infiltration in kwashiorkor was a transient phenomenon and that cases with similar signs and symptoms might or might not have an excessive amount of fat in the liver directed attention to other and more constant lesions (Davies, 1948a). At all ages, and in all stages of the disease, there was abundant evidence of a failure of digestion, masses of undigested food being present in the stools (p. 97). Normet (1926, 1937b; Bablet and Normet, 1937) had previously drawn attention to the lesions in the pancreas. It soon became apparent that the major damage was to that organ, the acinar enzyme secreting cells undergoing an intense acute atrophy, the secretory granules vanishing and the cells being reduced to little more than nuclei with a thin rim of surrounding cytoplasm.

Before going further, it should be emphasized that changes of this kind are not confined to the exocrine enzyme secreting cells of the pancreas. They are generalized throughout the body, probably affecting all cells which lose large quantities of secretion. Thus the salivary glands, the intestinal enzyme secretory glands and the lachrymal glands are all involved (Davies, 1951).

The most striking changes are seen in the pancreas because of its greater mass of secretory cells. With the liver and the small intestine it has the greatest protein turnover of the body tissues (Tarver and Schmidt, 1942). It is thus particularly vulnerable to protein deficiency. The development of the pancreas has been studied by numerous workers chiefly in relation to the development

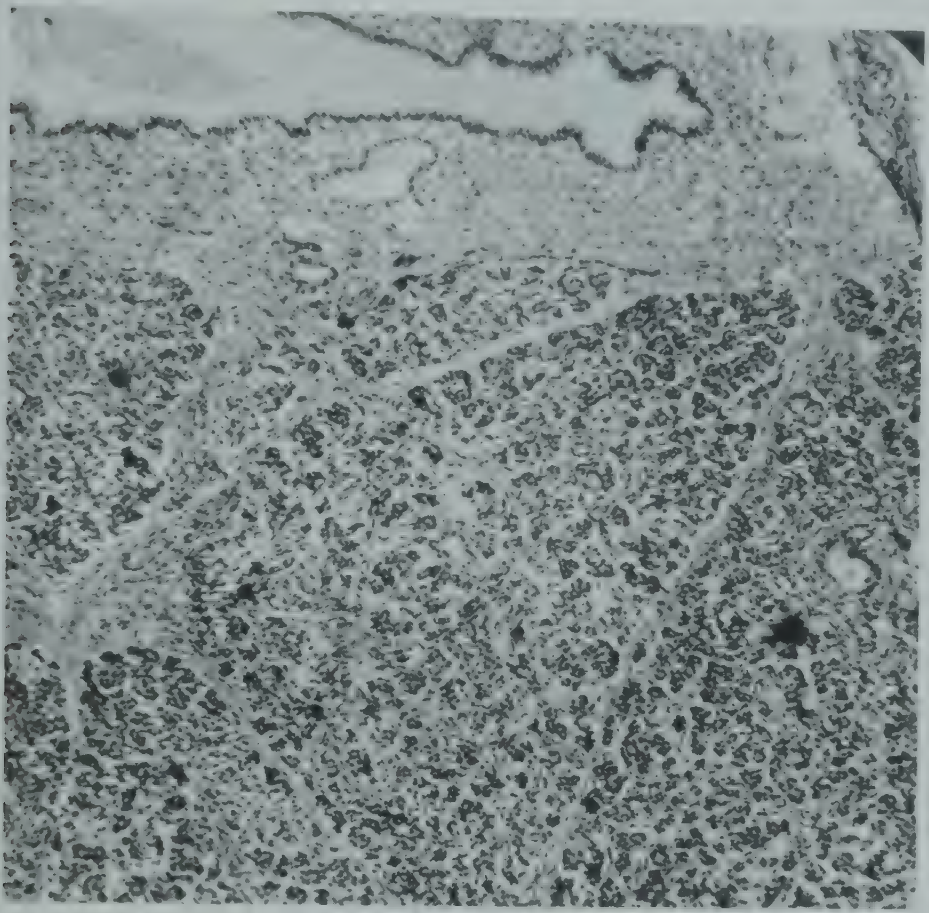


FIG. 14 (*a*).—Pancreas. Early kwashiorkor. Girl aged 18 months.

Showing gross acinar cell atrophy. No changes in the epithelium of the duct op of picture).

Stained with haematoxylin and eosin. Magnification × 75.

nd function of the islet tissue. As regards the acinar tissue there evidence that this is functional at birth and no evidence has been roduced of any critical lack of ability to produce enzymes even in remature babies. Emery (1951) has shown that normal lobulation nd the development of maturity in the pancreas may be delayed r many months in normal children and that a disproportionate nount of fibrous tissue may be present, particularly in early fancy. There is, however, no reason to suppose that at the weaning period of the African child the pancreas should not be structually and functionally normal for the age.

The atrophic changes in the pancreas have been repeatedly observed. The small size of the pancreas at autopsy is due to a shrinkage of the acinar cells (Fig. 14 (*b*)). The shrinkage is accompanied by a reduction in the number of enzyme granules and a loss of the basal pro-enzyme plate. The nucleus becomes closely adjacent to the basal membrane, and the cell continues to shrink closer to the basal membrane, producing the picture of a primary pancreatic atrophy (Nezelof, 1951). Finally in severe cases only cell clusters are seen, the remains of the acini : little but the nuclei are left, rings of nuclei along the basal membrane surrounded by narrow strips of clear cytoplasm (Fig. 15). Some of the cells may be vacuolated, possibly with fat, and others may contain small hyaline masses. In

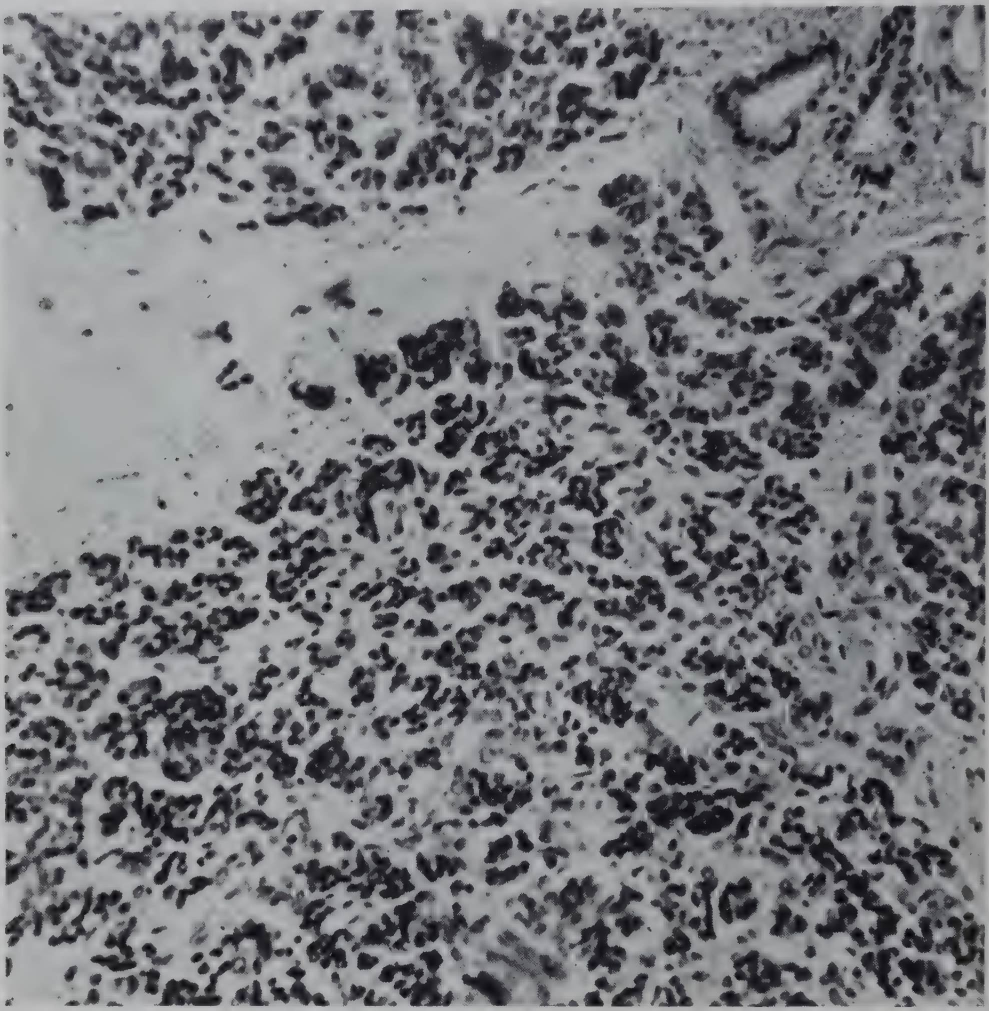
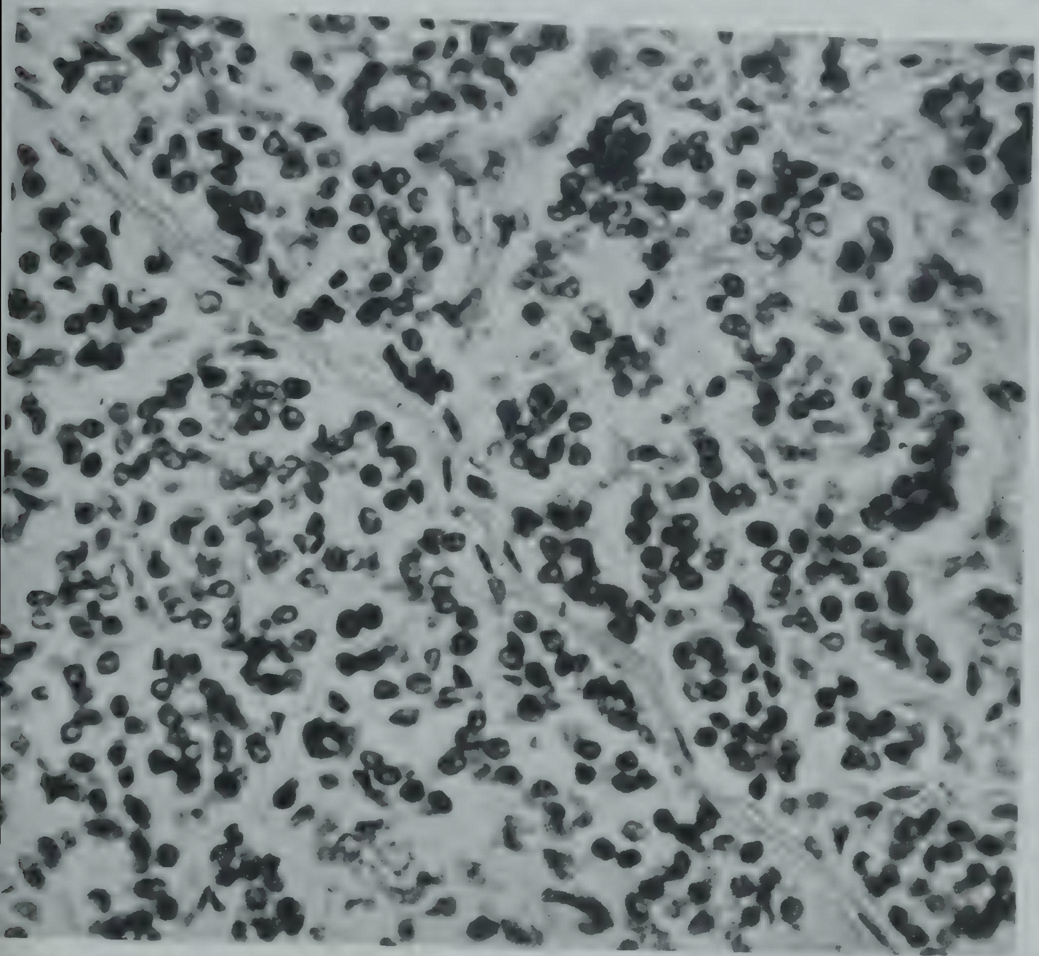


FIG. 14 (*b*).—Same pancreas as Fig. 14 (*a*). Showing gross acinar cell atrophy with prominence of the cells of the intercalated ducts.

Stained with haematoxylin and eosin. Magnification × 150.

ontrast, the intercalated ducts may be clearly visible and compose he greater part of the lobule with their pale-staining cells and narrow luct lumens (Hartz, 1949). Occasionally small amounts of inspissated secretion are present, but this is never a major feature.

The severe atrophy of the pancreas may be recognized even if



IG. 15.—Same pancreas as Fig. 14 (*a*). High-power view, showing gross acinar cell atrophy.

In the secreting cells the cytoplasm has almost disappeared leaving only the dark clei. The intercalated ducts are prominent and there is early increase of conctive tissue.

Stained with haematoxylin and eosin. Magnification × 300.

e autopsy has been delayed for some time, as autolysis takes place latively slowly.

It is now clear that the atrophic changes in the acinar cells of the ncreas are the most constant and persistent lesion in kwashiorkor, more so than the fatty liver changes (Davies, 1948a; Véghelyi, 50a; Camain and Pierchon, 1952). But they must be looked for tically. The extreme atrophy of the severe case is easily recogzed, but lesser degrees may easily escape notice.

The atrophy responds readily to a moderate improvement the diet. A few days feeding of even the usual African hospital di may result in an increase in the acinar cell cytoplasm with reappea ance of the enzyme granules. A few days feeding of a high protei diet may effect considerable alteration in the appearance of th pancreas while there is yet little visible change in the liver. There fore, unless it is looked for critically, and the speed of recovery i borne in mind, the pancreatic atrophy may be overlooked or under estimated and its importance may be unrecognized. The sensitivit to improvement of the diet is one of the reasons why for so man years the importance of the pancreatic lesions was not stressed.

In a few children who have died in the days immediately fol lowing the institution of a high protein diet the changes of regenera tion have been observed. They are not uniform throughout th pancreas, but here and there groups of acini seem to expand sud denly and to reform their secretory granules ; they compress thei neighbours, which in turn begin to swell and to reform their granule till the process is uniform throughout the pancreas. Such reacti vated cells appear to be larger than normal.

Some while after the atrophy of the pancreatic acinar cells ha become established there is often an increase in the amount of fibrou tissue in the pancreas. It is seen first around the acinar cell adjacent to the basement membrane and between the intercalate ducts. It increases in amount slowly and irregularly, being seen i some sections and not in others. In older children with kwashiorkor it is more apparent as a fine pervasive increase in the fibrous tissue of the pancreas (Davies, 1948a ; Hartz, 1949). A definite sclerosis of the pancreas which can be recognized by palpation of the gland at autopsy is uncommon in children, but is quite frequently encountered in adults, an observation confirmed by experience in other parts of Africa (Robert, Long, Feyte and Dareys, 1933).

Changes in the pancreatic ducts are not seen in uncomplicated kwashiorkor ; there is never any metaplastic change in the ductal epithelium and inspissated secretion is very infrequently found. Complicated cases of kwashiorkor, especially those dying with gastro-enteritis or severe infections, may show some evidence of the microcystic changes described by Baggenstoss (1948) and Hartz (1949). No true case of fibrocystic disease of the pancreas has been seen in African children in Uganda, and in no case of ashiorkor were there any changes resembling those seen in fibro- stic disease (Andersen, 1938 ; Farber, 1944 ; Bodian, 1952), either the pancreas itself or in the other organs. While the changes in the estine and the liver consequent upon the absence of pancreatic cretion from the intestine may be similar in the two diseases ebster and Williams, 1953), the conception that kwashiorkor has y pathological relationship to fibrocystic disease cannot be accepted. the latter disease, and also in marasmus, although the cells of the ncreatic acini may be slightly atrophic, they contain secretory anules in abundance and the enzymic content of the duodenal ice may sometimes be normal (McDougall, 1950).

It was predicted from a study of the histological changes in the ncreas that there would be a diminution of the content of pan- eatic enzymes in the intestine (Davies, 1948a). This has now en verified (p. 169). It was also suggested that, since in early ses there was found severe pancreatic atrophy and only moderate minimal fatty liver infiltration, the pancreatic atrophy preceded fatty infiltration. This was partially confirmed by Véghelyi 950a). He performed no liver biopsies, but he found that a minution of the pancreatic enzyme secretion preceded the enlarge- ent of the liver or any change in hepatic function. One pos- ility, therefore, seems to be that the children with kwashiorkor virtually depancreatized by dietary means, and that the fatty er infiltration is a consequence of the almost complete loss of ncreatic enzymes from the gut (Davies, 1948a). The lesions the liver bear a resemblance to those described in animals after gical pancreatectomy (Allan, Bowie, MacLeod and Robinson, 4). The pancreatic atrophy, therefore, appears to the writer be a more fundamental lesion than the fatty liver infiltration, ich it certainly precedes and which it outlasts in cases which are lequately treated. It appears to be present in every severe case washiorkor, though its appearance is often modified because it ensitive to relatively slight improvement in the diet.

(*ii*) *The small intestine.* In some conditions in which pancreatic etion does not enter the intestine its absence leads to less change he digestive capacity than might be expected, because the loss nade good by the secretion of the other enzyme-secreting cells of small intestine. However, in kwashiorkor there is evidence of a or failure of the digestive capacity, and the intestinal enzyme etion does not compensate for the lack of pancreatic secretion, because all digestive enzymes are partially affected by the atroph In the early stages there may be little or no macroscopic eviden of damage to the intestine save for oedema, but in more advanc cases the intestine wall becomes thin (tissue paper intestine) wi a smooth, atrophic mucous membrane (Passmore, 1947–48). T small intestine below the duodenum is most affected, but there little change in the colon. The changes are not so obvious in t duodenum because the Brunner's glands do not seem to underg much atrophy. Nor are the mucus-secreting goblet cells muc involved, and a considerable amount of mucus may be present the gut. The Paneth and other exocrine enzyme secreting cel undergo the same profound atrophy as the pancreatic acinar cel with reduction in size and lack of granularity. Later all the coa of the intestine are atrophied, the muscle being thin and pale wit occasional vacuolation of the fibres. No particular changes in th ganglion cells have been noticed, but special studies have not bee made.

The stomach shares in the atrophy of the alimentary tract bu histological studies have yet to be done. Here, as elsewhere in th intestine, superficial erosions may be present but haemorrhages ar unusual. The colon does not show any specific changes thoug the muscle coats may be atrophic, and a moderate degree of colitis with reddening of the mucosa and desquamation of the epithelium is often seen. The mesenteric lymph glands often show evidenc of a marked degree of sinus catarrh.

In both the pancreas and the intestine it is unusual to find an marked degree of cellular infiltration of the tissues, although occasional collections of lymphocytes may be found. The importan and fundamental lesion in the intestine would appear to be th atrophy and degranulation of the enzyme secreting cells.

(*iii*) *The salivary glands.* Atrophy of the salivary glands is no easily detected by clinical examination in children with kwashiorko because of the abundant subcutaneous fat and the oedema. Microscopic examination reveals that there is marked atrophy of th parotid gland (the submaxillary gland being less affected) due t shrinking and degranulation of the zymogen secreting cells (Fig. 16) the mucus secreting cells being less, if at all, atrophied. There ar no changes in the ducts or blood-vessels, and in the early stages ther is no cellular infiltration, though there may be an increased amoun of fat in the parotid glands. Fibrosis seems to start around th trophied and often dilated acini and the fibrous tissue may be nfiltrated with lymphocytes, especially in older children (Gillman, ilbert and Gillman, 1947). Sections of enlarged parotids such as re sometimes seen in the recovery stage of kwashiorkor (Davies, 948a; Thomson, 1950–51a) and which are seen in older children nd adults (p. 258), show great secretory granular enlargement of the cinar cells which stain very deeply. Mitotic figures are not seen and here does not seem to be any increase in the number of cells present,

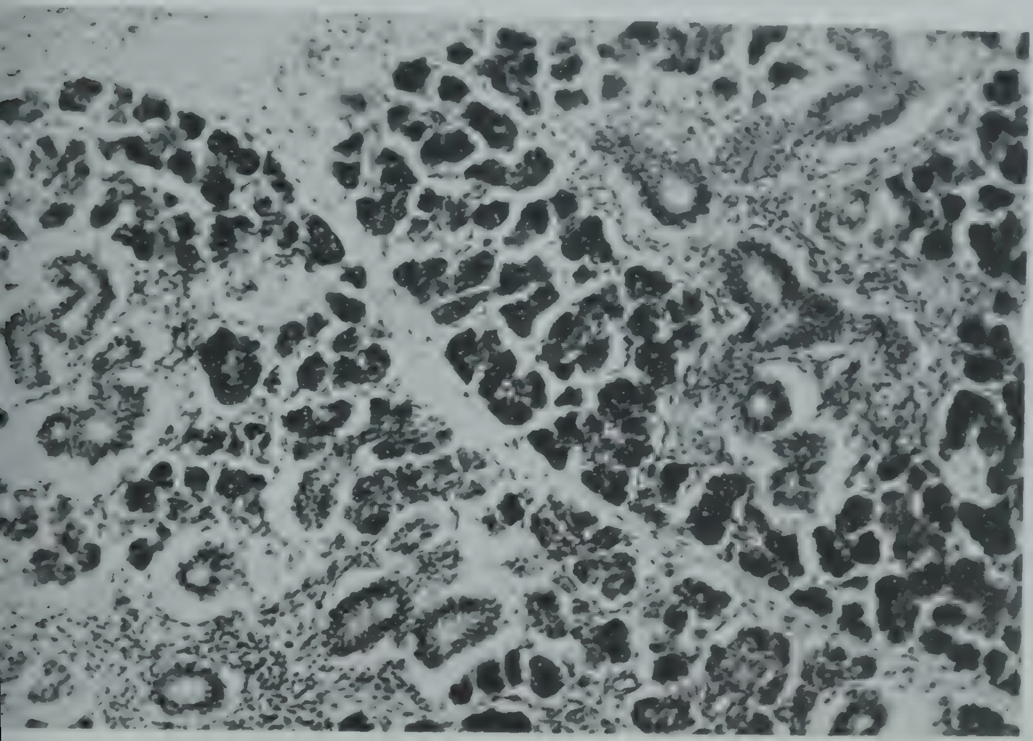


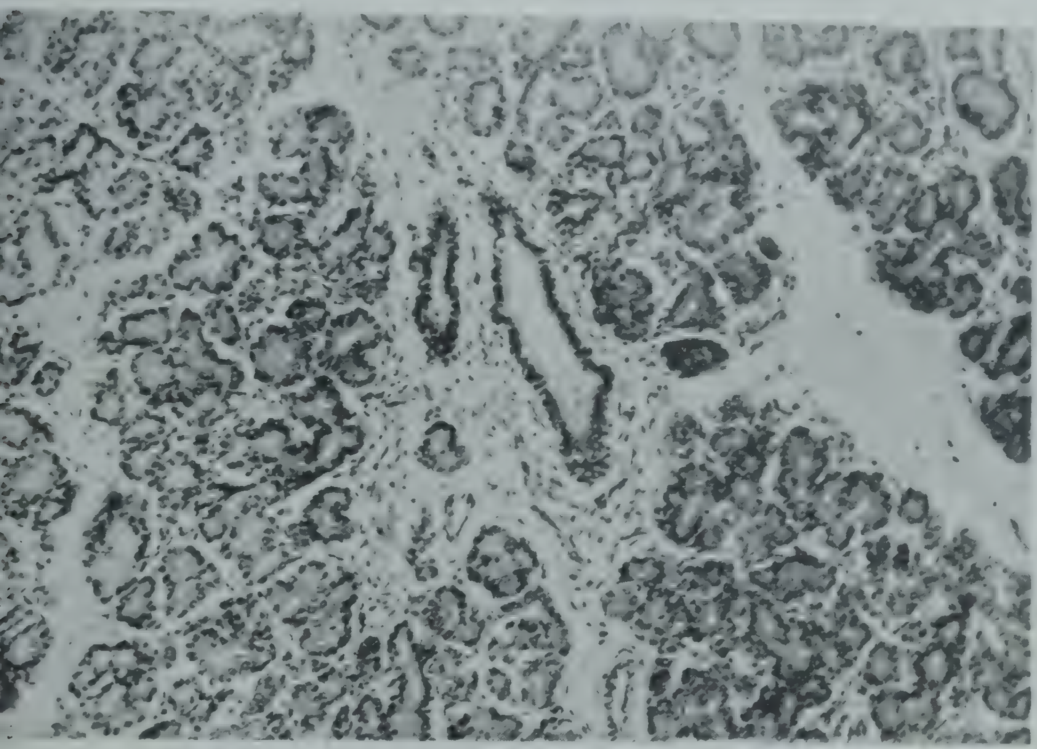
Fig. 16.—Parotid Gland. Girl, 1½ years old.

Showing atrophy of the secreting cells with some round cell infiltration. Stained with haematoxylin and eosin. Magnification × 120.

that the enlargement would appear to be a true hypertrophy follow- atrophy. Enlarged parotids are commonly seen in the adolescent l adult inhabitants of many tropical countries (Kenawy, 1937; n, 1947; Trowell, 1949), being commoner, perhaps, in the adults arkness, 1935–36), and such studies as have been made have all essed the absence of marked histological changes in the glands, ugh there may be some fibrosis and lymphocytic infiltration. otid enlargements have been studied in malnourished European lts, and the whole problem has been discussed by McCance, un and Barrett (1951). After pointing out that swelling of the otids has often been recorded after refeeding undernourished individuals, they describe histological studies of a single case which led them to the conclusion that the increase in size of the gland was due to an increase in size of the individual acinar cells, the whole of the cytoplasm being full of granules with the nuclei compressed towards the base. They concluded that this might represent a greater functional activity of the enlarged parotid and suggested a work hypertrophy, a response to over-feeding after a prolonged period of undernutrition. Swelling of the submaxillary glands is not usually apparent clinically, but their involvement is shown by histological evidence, and submaxillary gland hypertrophy was illustrated by McCance and his associates.

(*iv*) *The lachrymal glands.* McCance made no mention of changes in the lachrymal glands. Yudkin and Lambert (1922) described degenerative changes in the lachrymal glands in experimental xerophthalmia of young rats, which they at first presumed were correlated with functional derangement; later they concluded that the changes were of doubtful significance, although they felt that changes in other ocular glands might result in disturbances of secretion which might predispose to infection of the conjunctiva. Ross (1921) described cases of keratomalacia and *Mehlnährschaden* but did not examine the lachrymal glands histologically. In kwashiorkor the lachrymal gland undergoes an atrophic change in the same way as does the pancreas and parotids. There is shrinkage of the acinar secretory cells with the cytoplasm shrinking down around the nuclei (Fig. 17). Observations on the results of feeding have not been made, but the lachrymal glands, like the parotids, appear on direct inspection to be enlarged in many African adolescents and adults, and therefore it is reasonable to postulate that they are disturbed in this type of malnutrition. Presumably the secretion from the lachrymal glands is affected. If some degree of derangement persists it may be a factor in the great frequency of purulent and muco-purulent conjunctivitis (Blumenthal, 1950), in which malnutrition is suspected to be an important causal factor (Boase, 1952).

(*v*) *Summary of the changes in the exocrine enzyme secreting glands.* The type of changes seen in the pancreas, parotid and lachrymal glands, and to a lesser extent in the small intestine and the submaxillary glands where the exocrine enzyme secreting cells are less concentrated, would appear to be of similar type. There is a primary atrophy of the enzyme secreting cells with reduction in ie secretory granules, and if this condition persists fibrosis with mphocytic infiltration develops. The glands may swell when the



G. 17.—Lachrymal Gland. Showing moderate acinar cell atrophy. Girl, 3 years old.

Stained with haematoxylin and eosin. Magnification × 120.

et is improved ; this certainly happens to the parotid, probably ppens to the lachrymal and the pancreas, and is more doubtful in e case of the submaxillary glands. The swelling may be permanent.

) Changes in other internal organs

While pathological changes might be expected to be found in all sues in kwashiorkor, little detailed study has been given to organs ner than those previously described. This is partly because the anges appear of less importance macroscopically, and also because y are not so constantly found, and when detected are of more ıbtful significance.

(*i*) *The heart.* Normet (1937b ; Bablet and Normet, 1937) laid ticular stress upon the cardiac lesions, but they have attracted e subsequent attention. Yet such lesions as Normet described ranulation and vacuolation of the myocardial fibres with loss of nsverse striation and nuclei which are irregular, hypertrophied, ormed and often cigar-shaped or large nuclei with square ends—

are encountered frequently at autopsies on African children. The lesions are most apparent in the subendocardial muscle fibres of the ventricles, particularly the left ventricle, which at autopsy often has a rather glazed appearance like that of the endocardium. There may be small interstitial collections of lymphocytes and macrophages, but these are uncommon. The vacuolation of the fibres is watery in character, and one which commences as an inter-fibrillary oedema and is not a fatty infiltration, though occasionally the latter may be present to some degree. The non-vacuolated fibres may be thin and atrophic. Occasionally the ventricles may contain adherent mural thrombi. These lesions may be related to electrocardiographic changes recorded (p. 101). They are perhaps more notable in adults. They assume considerable importance in relation to the pathogenesis of the syndromes of nutritional heart disease in Africans (Davies, 1948b, 1951 ; Gillanders, 1951 ; Higginson, Gillanders and Murray, 1952).

(*ii*) *The kidney.* Cloudy swelling and fatty infiltration of the tubular cells with cytolysis and pycnosis of the nuclei is usually found in severe cases of kwashiorkor (Smith, 1942–43), and glomerular sclerosis and hyalinization is very frequently seen but is of uncertain significance (Davies, 1948a). Raper (1952) suggested that the sclerotic changes are most often found in groups of glomeruli arising from a single interlobular artery and arranged in an arborescent pattern. He thought it was probably due to a vascular blockage and that it was associated with, and possibly due to, the presence of sickling red corpuscles. This, however, may not explain all cases. In older children the epithelial cells lining the Bowman's capsules often tend to be cubical, especially near the entrance of the proximal convoluted tubules, but this is a common finding in the kidneys of Africans, both children and adults. Crescent formation is not seen but the capsular spaces may contain eosinophilic coagulum, as may the tubules, and a degree of pericapsular fibrosis is common. Hyalinization usually starts at the base of the glomerular tuft. The changes in the kidney, though irregular and consistent, may well be an important feature of the disease. They bear a distinct resemblance to the renal changes in the so-called ' idiopathic ' albuminurias (Rather, 1952) and those which accompany portal cirrhosis of the liver (Baxter and Ashworth, 1946) in man, and in animals.

(*iii*) *The spleen.* Though Normet (1928, 1937b ; Bablet and

ormet, 1937) in his early descriptions paid particular attention to
sions in the spleen it was later concluded that these were non-
pecific, being due to associated parasitic infestations, particularly
alaria. There seem to be no specific lesions of the spleen though
e malpighian bodies may share in the general atrophy of the
mphoid tissue seen in malnutrition (Jackson, 1925).

(*iv*) *The brain.* Changes in the brain have not been made the
bject of special study and it is not known if there is any histo-
gical counterpart to the striking mental changes. As previously
entioned, there is often oedema and congestion of the brain at
topsy.

(*v*) *The skeletal muscles.* Waterlow (1948a) reported that the
uscles were shrunken and small, that the fibres were atrophic and
at there was gross loss of sarcoplasm, the fibres having shrunk
ay from the surrounding perimysium so that in cross section
e nuclei were seen to be surrounded by only a thin rim of cyto-
asm. Experience in Kampala agrees with Waterlow's observa-
ons. It has also been noted that the transverse striations in
luntary muscle are often blurred and indistinct and that hyaline
generation, resembling a Zenker's degeneration, is not uncom-
on. The smooth muscle of the intestine may become very
rophic.

(*vi*) *The endocrine glands.* It was suggested by Normet (1937b;
ablet and Normet, 1937) that the islets of Langerhans were often
rophic, but Hartz (1949) stated that they were of normal size and
ight appear enlarged by comparison with the atrophied acinar
lls. Camain and Pierchon (1952) said that while acinar cell
ophy of the pancreas was invariable in kwashiorkor the increase
fibrous tissue, and hypertrophy of the islets, were variable. The
ets do not seem to have actually been measured, and no cytologic
anges have been mentioned. The thyroid is atrophied; the
ount of colloid is diminished, and the vesicular cells are flattened
l inactive. It is probable, from the studies of Vint (1949) on the
rican pituitary, that there are changes in this gland, but no detailed
dy has been made in kwashiorkor. Vint (1936–37) drew atten-
to the profound atrophy of the thymus, which is often so great
t the gland cannot be recognized. The developing gonads have
been studied. In the adrenals Trowell (1937) noted " haemor-
ge in the zona reticularis in two cases in which the glands were
erwise normal in appearance but slightly enlarged in size and

weight". Bablet and Canet (1952) have stressed the adrenal changes; they found the adrenals enlarged and fragile, and the cortical cells full of fat. Congestion and sclerosis of the medulla were common. Houssiaux (1953) also noted similar changes. More usually, however, in Kampala experience, there is marked atrophy and absence of lipoid in the cortex, the zona glomerulosa being extremely atrophic (Fig. 18). There may be scattered groups of more active glomerulosa cells, sometimes in the form of small extra-capsular adenomata, and there may be an excess of fibrous tissue spreading inwards and accompanied by thin strands from the capsule. Pigment is usually absent from the juxta-medullary zone and the medullary cells themselves are often atrophic.

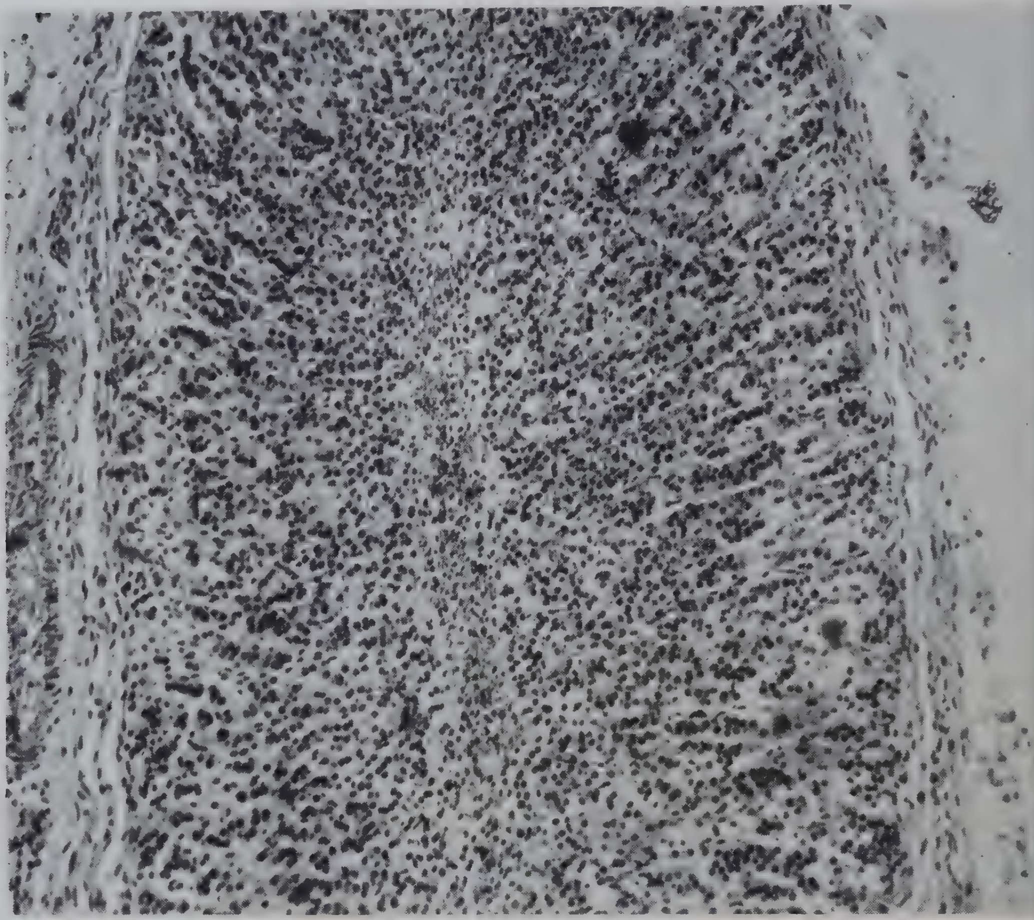


FIG. 18.—Adrenal. General view of whole thickness of the gland. Boy, aged 2 years. The cells are all small and there is little lipoid present. Stained with haematoxylin and eosin. Magnification × 75.

(*vii*) *The lungs.* Pneumonic changes are present at autopsy in the majority of cases dying of kwashiorkor. They present no special features, save that often the polymorphonuclear cells in the xudate are not as plentiful as might be expected, and there are often large number of macrophages present. Considerable number of acrophages are usually seen in the lungs even when no obvious nfection is present. Pulmonary oedema, often severe, is frequently een, but hyaline membranes have not been observed, and there are one of the changes in the bronchial epithelium or mucous glands ecorded in fibrocystic disease of the pancreas.

) Bone pathology[1]

The ribs of Bantu infants dying with the stigmata of kwashi- kor frequently showed " beading " of the costochondral junctions. several cases the ribs appeared more easily bent or cut than those om comparable European subjects.

The most significant lesions noted on microscopical examina- on were essentially those of growth depression. The severity of e depressive changes varied and were probably dependent on the ngth of the period of malnutrition. In those cases with most arked changes the zone of endochondral ossification was often duced to less than half of the expected width and the area of lcified cartilage, as demonstrated by Ehrlich's haemotoxylin, also peared diminished. The number of both columnar and hyper- ophied cells was decreased, the cells themselves being flattened ith pycnotic nuclei. In the sub-epiphysial zone vascular invasion the calcified cartilage had ceased and the metaphysial trabeculae ere absent or short and club-like. Sometimes, the spaces formed the degeneration of hypertrophied cells contained a plug of sified material and were separated from each other by projections epiphysial cartilage covered by a thin layer of bone. The osteo- asts were spindle-shaped and their activity was slight. Osteoclasts re few or absent. In the shaft the trabeculae often appeared enuated and reduced in number (Fig. 19, (*a*), (*b*), (*c*)).

In ribs where growth depression was less marked the changes re confined to unequal capillary invasion of the epiphysis and luction in the number of proliferative cells.

In the majority of cases transverse trabeculae were not prominent, in one case observed the epiphysis was sealed on the meta- sial side by prominent transverse trabeculae, forming a line of sted growth. The bone marrow usually appeared normal but

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[1] This section has been contributed by Dr. John Higginson, of the th African Institute of Medical Research, Johannesburg.

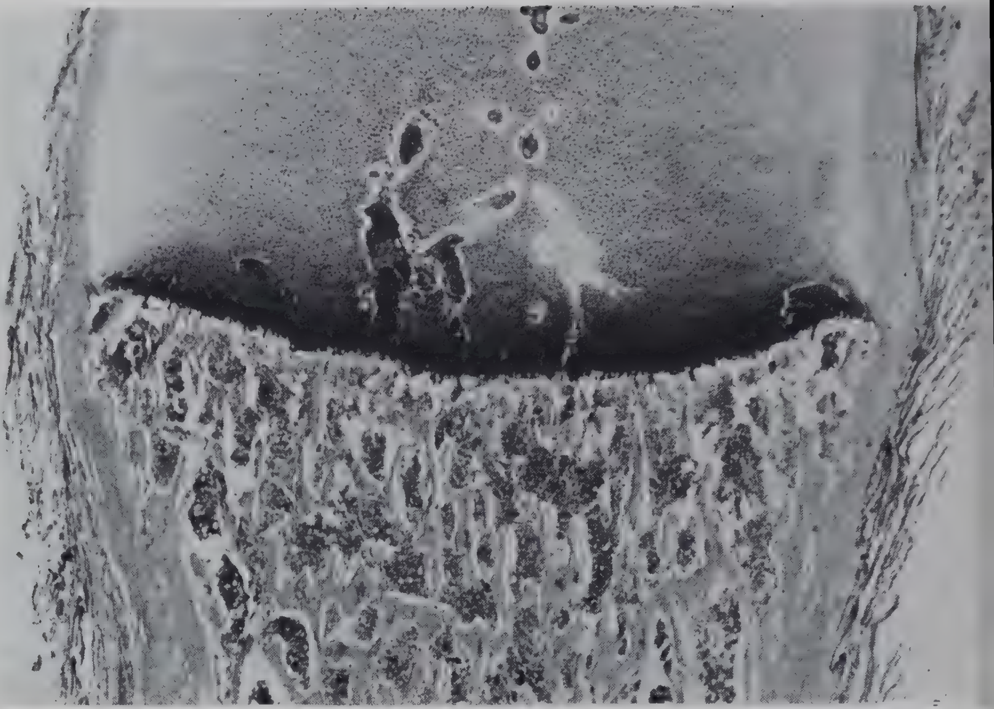


FIG. 19 (*a*).—Costo-chondral junction of Bantu girl aged 8 months, dying from kwashiorkor with oedema, a desquamating rash and fatty changes in the liver.

There is marked growth depression, with almost complete absence of capillary invasion of the metaphysis. At the junction of shaft and cartilage the trabeculae are few and attenuated. Stained with Ehrlich's haematoxylin and eosin. Magnification × 15.

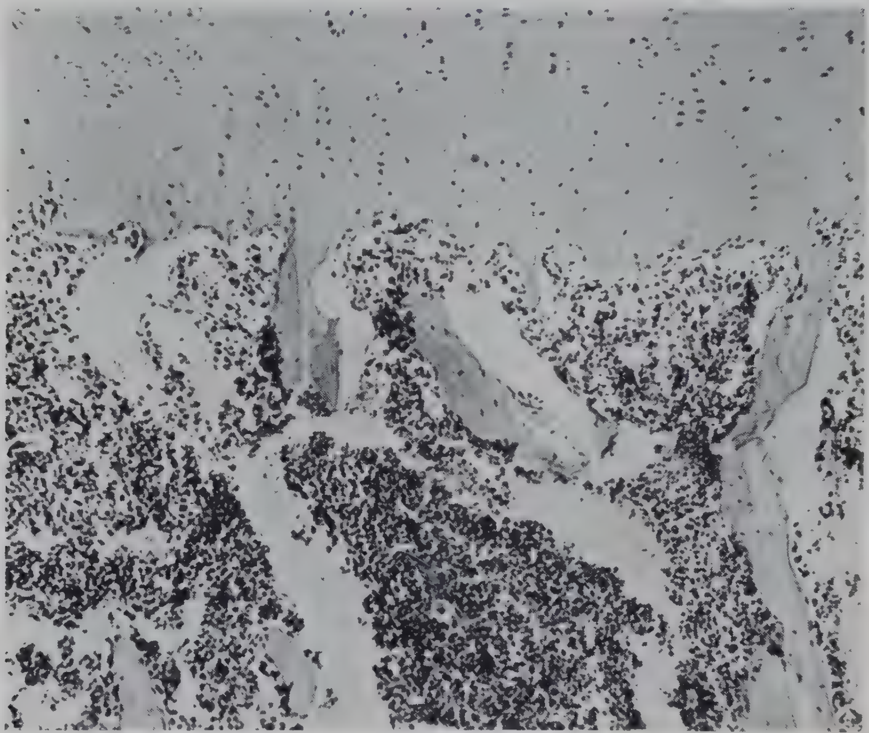
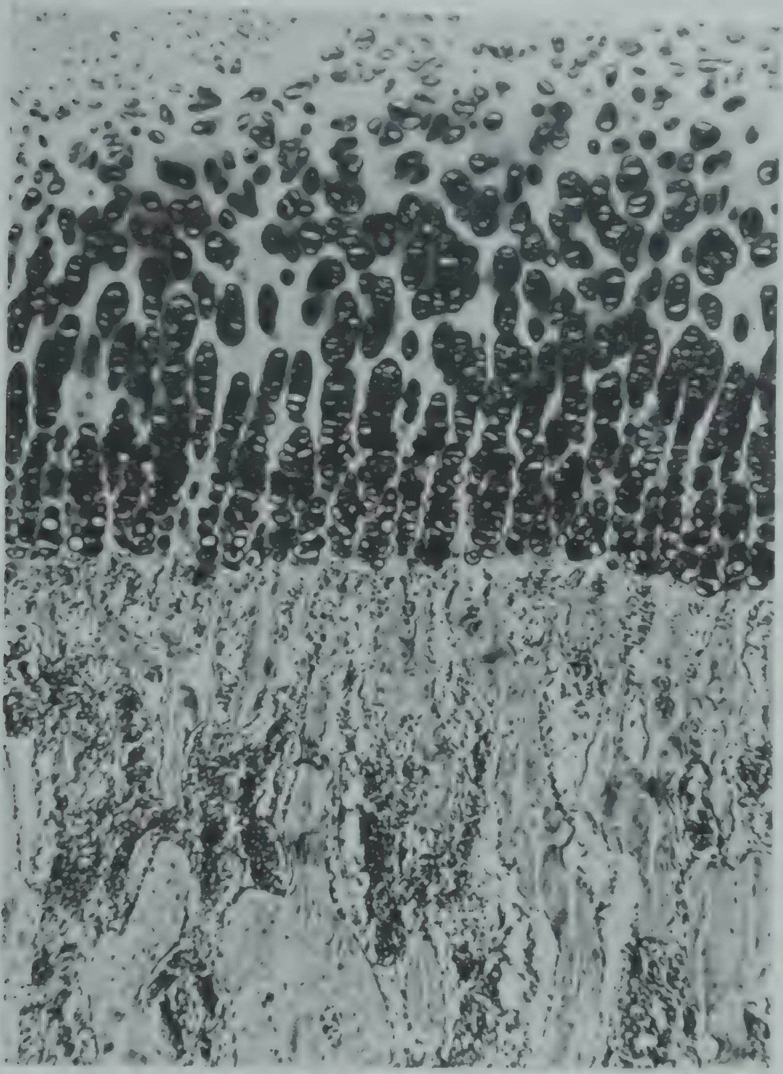


FIG. 19 (*b*).—High-power view of the same rib as in (*a*). The absence of capillary invasion is very striking and there are very few proliferating cartilage cells. There is no osteoblastic activity in the shaft and no osteoclasts are present.

Stained with Mayer's haemalum and eosin. Magnification × 105.

marked decrease in red marrow was noted in one rib. In only ne rib was osteoid observed in the metaphysial region. In this se there was also irregular invasion of the epiphysial cartilage hich showed degenerative changes.

Chemical estimation of the bone ash of ribs from kwashiorkor



. 19 (*c*).—Normal costo-chondral junction of European girl aged 12 months, dying from gastro-enteritis. For comparison with Fig. 19 (*b*).
Stained with Ehrlich's haematoxylin and eosin. Magnification × 105.

rs[1] has shown the same range as that observed in European nts dying from trauma and other causes.

The lesions described above are not specific for kwashiorkor but those of severe growth depression. In a series of ribs from

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By Dr. A. R. P. Walker, of the South African Institute of Medical arch.

Bantu and European children examined by me, however, only Bantu infants dying from diarrhoea and vomiting associated with malnutrition showed depressive growth changes of comparable severity. A similar pathological picture has been produced in guinea-pigs, by underfeeding (Silberberg and Silberberg, 1940), and in rats, by a protein-deficient diet (Follis, 1950).

(*e*) Changes in the skin

Great attention was formerly paid to the dermatosis of kwashiorkor, probably more than it deserved, for it is variable and is often absent except in advanced cases. There may be a considerable increase in the amount of pigment present, the increase being distributed throughout affected portions of the epidermis, especially where there are areas of hyperkeratosis. The rete pegs may be very long and irregular with fusion of their tips. The hyperkeratotic areas tend to come away from the corium over large areas. Elsewhere there may be atrophy of the whole epidermis with irregular shortened and flattened rete pegs (Waterlow, 1948a), particularly in the flexural areas. The changes have been studied in great detail by Gillman and Gillman (1951), who summarized them as a loss of pigment from the melanoblasts, the subsequent accumulation of pigment in the outer layers of the epidermis, impairment of normal cornification, and then desquamation. Gillman and Gillman decided, on the basis of the histological changes, that the enamel-paint dermatosis of kwashiorkor in young children was very similar to the skin changes seen in severe cases of classical pellagra in African adults (p. 117). Berthe, Bergouniou and Raoult (1952 *Proc.*), however, concluded that there was no characteristic lesion of the skin in kwashiorkor and suggested that the lesions described in various countries were mainly the result of the severity and the rapid development of skin oedema.

(*f*) Summary and discussion of the histopathological changes

The pathological studies which have been made of cases of severe kwashiorkor in childhood reveal a remarkably consistent pattern of changes. The pancreas, salivary glands, lachrymal glands and the small intestine all undergo atrophic changes. There is a wasting of the muscles and of protoplasm generally, the liver cells being particularly affected. On top of the hypoplastic changes in the liver is superimposed a fatty infiltration which may be severe but tends to be transient. The atrophic processes are associated ter a time with a sclerosis of the major affected organs ; there is a ne fibrosis in the liver, pancreas and salivary glands which tends to ersist despite clinical improvement. The gross oedema and the her changes suggest such profound alterations that it would seem rtain that all organs of the body must be affected to a greater or sser degree, but many organs have not yet been studied.

The most significant of the pathological lesions seems to be a lective atrophy of the acinar cells of the pancreas with a loss of eir zymogen granules. The primary lesion is not the cellular rophy, but is rather a failure of formation of the enzyme granules : e granules, which are normally produced in the cells and subquently discharged, are not re-formed as they should be. No eficiency of calories, vitamins or minerals is known to produce is lesion.

The problem considered from the aspect of pathology can there- re be narrowed to a study of the factors which govern the formation the secretory granules. The granules are largely, if not entirely, otein, and their formation must depend on a liberal supply of otein, whatever other factors are involved. The pancreas shares ith the small intestine the distinction of having an extremely high rnover of nitrogen, presumably because secretory activities impose great drain of protein.

It is reasonable to assume that in kwashiorkor, so long as the take of food is maintained there is a call for pancreatic enzymes. he granules are used up and cannot be replaced, and finally the lls atrophy. Because the intestinal cells are also affected, the ficiency of pancreatic secretion cannot be compensated and the sults are very serious. The basic pathological lesions can there- e be explained, without invoking unknown factors (and avoiding cam's razor) on the basis of protein deficiency. It does not help postulate a primary failure of substances stimulating secretion the pancreatic cells because the substances are probably protein- eous themselves. Some evidence obtained in animal experiments ds to the same conclusions about the importance of protein iciency. A low protein diet fed to rats produced atrophy of the ncreatic cells (Friedman and Friedman, 1946), and a low protein, h carbohydrate diet, similar to diets on which children develop ashiorkor, has similar effects (Kristal, 1947).

It is not known what specific amino acids are essential for the duction of pancreatic enzymes. The work of Samuels (1948, personal communication) suggests that *iso*-leucine may be important, since a deficiency may produce pancreatic atrophy, and recent studies of the action of ethionine by a number of workers, which has similar effects, point to methionine (ethionine being an antimetabolite of that amino acid). The possible importance of the sulphur-containing amino acids (of which methionine is one) in enzyme activity in kwashiorkor is discussed elsewhere (p. 223). Kwashiorkor is unlikely, however, to be the result of a lack of one, or even a few, of the amino acids : probably many amino acids are simultaneously involved, although a loss of powers of interconvertibility may increase the need for one or more in particular.

In kwashiorkor, the fat which is deposited in the liver always appears first at the periphery of the hepatic lobule. It is probable that in no other disease of man, and in no condition produced experimentally in animals, is the fat found invariably in this position (Gyorgy, 1952, personal communication). It was found possible at Kampala to induce fatty livers in weanling rats by feeding the staple food of the district, the cooked banana (plantains), but the fat appeared to be deposited first in the part between the periphery and the centre of the lobule. The diet, although low in protein and high in carbohydrate, did not cause fatty livers unless the diet of the mothers had been vegetarian, and the deposition of fat could be almost, or completely, prevented in the weanlings by adding vitamin B_{12} or some methionine to the banana, or by giving a high-protein diet, rich in vitamin B_{12}, for a few days (Dean, to be published). It was also found that the banana diet, even if it did not cause large accumulations of visible fat in the liver, seemed to affect a function which is usually ascribed to the liver—the destruction of anti-diuretic hormone produced by the pituitary. It is not possible to say at the moment how far these experiments reproduced the changes found in kwashiorkor, but the connection is obviously worth pursuing. The difference in the sites of deposition of the fat within the lobule may be no more than a species difference, or it may have some other significance ; Best (1950) believes that fat of dietary origin and fat drawn from body depots can be distinguished by the sites that are occupied.

The child with severe kwashiorkor has been described as virtually depancreatized, and has been compared to the depancreatized dog. The similarity should not be pushed too far for various reasons, including the acute nature of the lesions in the dog, and the hronic nature of the process in the child. In the dog maintained n insulin, the removal of the pancreas is followed by a slow ccumulation of fat in the liver; afterwards, the fat is slowly emoved, with an increase of fibrous tissue gradually becoming pparent. In the child under treatment for kwashiorkor, clinical nprovement seems to proceed more rapidly than the removal of ver fat (Meneghello, Espinosa and Coronel, 1949). The opporinities for observing the course of events in untreated kwashiorkor e naturally very few, but the routine study of autopsy tissues at ampala suggests that fatty livers are most common during the cond and third years of life, and that as the years pass the amount fat decreases and fibrosis begins to show. The tempo of the ents has not been exactly established, and it is not known whether a eriod of protein malnutrition in the later years leads to fresh ncreatic atrophy and a new wave of fatty infiltration of the liver.

The fatty liver may be a result of derangement of the pancreas, it other explanations are possible; the diets producing kwashikor may lack substances which prevent the deposition of fat, or able the fat to be mobilized, or there may be a failure of enzyme stems which are unrelated to these substances.

Finally it must be admitted that although all the histological idence at present available points to the pancreas, rather than the er, as being the first organ to be affected in kwashiorkor, there is e possibility that a transient episode of fatty infiltration of the liver ay be the first event: a short period of increased fattiness has en noticed in mice within a few days of the start of a low protein et (Heller, 1953, personal communication). It would probably ed finer tests than are at present known to show if the liver (or, deed, the pancreas) is affected very early in the genesis of kwashikor. An attempt to explore this possibility should certainly m part of any investigation of mild cases (p. 110).

THE BIOCHEMICAL FINDINGS IN SEVERE KWASHIORKOR

The serum proteins

In the severe stage of kwashiorkor the serum chemistry suggests a iod of protein deficiency. The simplest manifestation, and the which has been most consistently studied, is the level of the total um proteins. A summary of some of the findings by various

TABLE 2

Total protein, albumen and globulin in the serum in acute kwashiorkor
(All values are for g. protein/100 ml. serum)

Author	Number of estimations	Total protein (mean and range)	Albumen (mean and range)	Globulin (mean and range)	Albumen/ globulin ratio (mean)
Achar and Benjamin (1953)	40	4·38 (2·81–5·98)	2·19 (0·85–3·98)	—	1·00
Altmann (1948)	20	4·20 (3·1–6·4)	2·1 (1·4–3·5)	2·1 (1·4–3·5)	1·00
Carvalho, Pinto, Schmidt, Potsch and Costa (1945)	50	4·09 (2·59–6·64)	1·89 (0·9–3·10)	2·15 (1·10–3·60)	0·95
Dean and Schwartz (1953)	33	3·98 (2·90–5·10)	—	—	—
	18	—	1·51 (0·76–2·17)	2·44 (1·68–3·62)	0·67
Delon (1951)	10	4·70 (3·9–5·3)	2·57 (1·65–3·29)	2·13 (1·30–2·55)	1·21
Janssen and le Roux (1950a)					
Series (*a*)	18	4·07 (3·12–5·11)	1·98 (1·30–2·65)	2·09 (1·37–3·49)	0·95
Series (*b*)	23	4·20 (3·04–6·09)	2·09 (1·42–3·57)	2·11 (0·50–3·79)	0·95
Van Der Sar (1951)	31	4·17 (2·40–5·40)	—	—	—
	15	—	2·18 (1·71–3·00)	1·99 (1·18–2·58)	1·10
Jayasekera, de Mel and Cullumbine (1951)					
(*a*) Children who died	13	5·53 (2·96–8·89)	2·55 (1·35–3·78)	—	1·05
(*b*) Children who survived	27	5·86 (2·42–8·19)	2·92 (0·30–4·75)	—	1·25

The method of separation of proteins used by Dean and Schwartz (1953) was precipitation of the globulin by 26% sodium sulphate, and Kjeldahl estimation of the nitrogen in the precipitate. Janssen and le Roux (1950a) precipitated with 23% sodium sulphate and then used a Nesslerization procedure. Jayasekera *et al.* precipitated with saturated sodium sulphate, and also used Nesslerization (King,

hors is given in Table 2. There is a considerable measure of
eement ; the total is usually depressed to about an average figure
4·0 to 4·5 g./100 ml. serum. The Kampala figure for one series
selected, uncomplicated cases (Dean and Schwartz, 1953) was
8 g./100 ml.

The table also gives details of some of the results that have been
ained when the albumen and globulin of the serum have been
ermined separately. It is clear that in acute kwashiorkor the
ount of albumen is greatly reduced, but that the amount of the
al globulins is as high as is usually found in healthy American or
ropean children. In 18 of the Kampala cases, the albumen
raged only 1·51 g./100 ml., which is about 3·0 g. lower than the
ue commonly found, and the globulin averaged 2·44 g./100 ml., a
ly high value. The albumen/globulin ratio was therefore 0·67,
ch below the normal range of 1·5 to 2·5. It should be
nembered, however, that the fractionation of serum proteins is
oriously liable to give answers which vary according to the
thod used. As different methods were undoubtedly used by
authors referred to in Table 2 (the methods were not usually
cified), it may be said that the results are on the whole reasonably
sistent.

There have been no serious attempts to correlate the degree of
ression of the total proteins, or of the albumen, with the severity
he condition of the child. The agreement is, for many reasons,
kely to be exact, but it was noticed at Kampala that in those
dren who appeared to have the most oedema (shown by the
unt of weight they subsequently lost) the serum proteins were
er than in those who had less oedema. Thus 11 of 18 children
se weight loss was 10 per cent or less of their weight when the
ma had disappeared had albumen values averaging 1·84 g./100
The average figure for the other 7 children, whose weight
s were between 12 and 32 per cent, was only 1·30 g./100 ml.
nderson and Altmann (1951) used the free Tiselius method for
stimation of serum protein fractions, and Table 3 shows the
lts they obtained from 6 children they bled early in treatment.
e children, whose total serum proteins averaged 4·0 g./100 ml.
nost exactly the Kampala figure mentioned above—had approxi-
ly 38 per cent albumen, 15 per cent α-globulin, 17 per cent
bulin and 30 per cent γ-globulin. By the normal (American)
lard quoted for comparison there were, in addition to the large

decrease in the albumen, a decrease in the percentage of α-globuli and an increase in the percentage of β-globulin ; these were small but there was a very large increase in the percentage of γ-globulin the actual *amounts* of the four fractions (albumen, α, β and γ-globulin were 35, 53, 84 and 230 per cent of the amounts in the America sera. For the six children the average albumen/globulin ratio wa only 0·61, a very low figure suggesting that the children may hav been comparable, in the degree of severity of their illness, with th Kampala children whose average was 0·67. The values should no

TABLE 3

Components of sera from untreated cases of kwashiorkor (called " malignant malnutrition ") analysed by free electrophoresis
(Data selected from Anderson and Altmann, 1951)

Case No.	Total g./100 ml.	Albumen %	Globulin α %	β %	γ %	A/G ratio
3	3·8	40·9	15·8	8·6	34·7	0·69
8	3·6	32·5	16·5	22·0	29·1	0·48
10	3·6	29·6	12·5	20·8	35·0	0·43
11	5·1	42·9	12·9	15·4	28·9	0·75
12	4·0	38·6	17·8	17·5	26·1	0·63
13	4·0	44·0	14·0	15·3	26·3	0·79
Average	4·0	38·1	14·9	16·6	30·0	0·61
Average of normal American children 1 to 4 years old (Knapp and Routh, 1949)	7·2	61·7	19·6	11·5	7·1*	1·64

The data were selected from Anderson and Altmann's tables because the were from fatal cases (Nos. 3 and 8) or the first of a series from the same chil (Nos. 10 to 13; see also Table 12, p. 212).

The amounts of the fractions in Knapp and Routh's cases were 4·37 g. albumen 1·13 g. α-globulin, 0·80 g. β-globulin and 0·52 g. γ-globulin ; the 4·0 g. of tot protein of the six African children contained 1·53 g. albumen, 0·60 g. α-globulin 0·67 g. β-globulin and 1·20 g. γ-globulin (see text).

* Includes 3·8% θ-globulin and 3·3% γ-globulin.

however, be compared too closely, because it is a well-known fac that the values for the ratio obtained by Tiselius fractionation ar usually somewhat lower than are obtained by chemical method such as those employed at Kampala.

The method of separation of protein fractions by electro phoresis on filter paper has been used at Kampala, and some result obtained by Dr. M. D. Thompson are shown in Table 4. Th amount of β-globulin is smaller than was found by Anderson an Altmann (Table 3), and the amount of γ-globulin is correspondingl gher. Dr. Thompson has found good agreement between the iper method and micro-electrophoresis in the Antweiler apparatus, cept that the apparatus gives a higher estimate of the α-globulin. he apparatus has been used by Close (1953) in the Belgian Congo. sera with an average total protein of approximately 4·0 g. 100 ml., found 26·8 per cent albumen, 27·7 per cent α-globulin, 9·2 β-obulin and 36·2 γ-globulin. The most considerable difference from e Kampala figures is in the α-globulin fraction, which is 11·0 per nt greater in Close's results, but this may be due to the apparatus.

TABLE 4

mponents of sera from untreated cases of kwashiorkor analysed by electrophoresis (paper separation)

(Data from Thompson, 1953, personal communication)

me	Total g./100 ml.	Albumen %	Globulin α %	 β %	 γ %	A/G ratio
	4·38	46·9	13·9	7·0	32·1	0·88
l	4·75	33·1	11·6	8·4	46·8	0·49
bu	4·02	35·9	17·6	13·5	33·0	0·56
g	3·50	38·9	11·4	5·7	43·8	0·64
b	3·65	22·0	34·6	9·0	34·7	0·28
r	5·10	40·9	16·7	5·8	36·6	0·69
m	4·38	43·1	14·0	9·3	33·6	0·76
n	4·02	22·9	10·3	8·3	58·4	0·30
mu	3·50	28·9	18·7	12·8	39·7	0·41
ba	5·84	35·7	17·1	8·2	38·8	0·56
ean *	4·30	34·8	16·6	8·8	39·7	0·56
D.	*0·71*	*7·8*	*6·6*	*2·5*	*4·5*	*0·19*

* The mean amounts of the protein fractions in 100 ml. serum were 1·52 g. umen, 0·71 g. α-globulin, 0·37 g. β-globulin and 1·71 g. γ-globulin. Compare ble 13.

Urea

Although it is usually maintained that the level of urea in the dy fluids of man is not subject to large variations, it seems that some circumstances low protein diets can bring about a conerable fall; adults given such diets by Schwartz, Thaysen and le (1952) had an average blood urea of only 8·2 mg. 100 ml., ich is far below the level of 25 to 35 mg. 100 ml. usually conered normal. Low values of the order of 12 to 15 mg. 100 ml. e also been reported in kwashiorkor; at Kampala an average of 2 mg. 100 ml. was found. Delon (1951) thought that a level of mg. 100 ml. had a serious prognostic significance, as it indicated ormal nitrogen retention. Chaudhuri's (1948) values for nontein nitrogen (28 to 45 mg. 100 ml.) seem to be higher than is be expected from his figures for blood urea.

3. Cholesterol

Several workers (Carvalho *et al.*, 1945 ; Delon, 1951 ; Dean and Schwartz, 1953) have found concentrations of total cholestero of the order of 80 to 120 mg./100 ml. serum, well below the level of 160 to 170 mg./100 ml. said by Behrendt (1949) to be usually found in young children. The normal ratio of free to total cholesterol is 0·2 to 0·3. The high ratio of 0·76 was found at Kampala ; it was presumably an indication of low activity of the cholesterolesterase described by Sperry (1935).

The level of total cholesterol in the blood is believed to be related to the amount of fat which the diet has contained. Low levels may therefore have no specific value in the diagnosis of kwashiorkor, unless they can be shown to have no connection with a deficiency of fat or cholesterol in the diet. It is perhaps worthy of note that van Oye and Charles (1952b) found the low average value of 93 mg. total cholesterol/100 ml. in the serum of 180 Bantu children, aged from 9 to 15 years, examined at Leopoldville. Jayasekera *et al.* (1951) found the surprisingly high level of 162 mg./100 ml. in 40 children aged 1 to 7 years who had kwashiorkor, although the home diets apparently contained very little fat.

4. Enzymes

(*a*) *Serum enzymes.* Amylase, thought to be largely of pancreatic origin, and esterase, were estimated in the serum at Kampala, and the levels in the acute state of kwashiorkor were found to be very low. In 12 of 14 children, the level of amylase was < 25 Somogyi units, and it was only 40 and 55 units in the other two. The esterase level, defined in terms of ability of the serum to split phenyl benzoate, was only about one-third of that found in more healthy children. Pseudo-cholinesterase activity was also low ; under the conditions of the experiments, in which the electrometric method of Michel (1949) was used, the average depression of *p*H was about one-quarter of that to be expected in normal children. Similar results were reported by Waterlow (1950) who used a manometric method in the investigation of the plasma of 20 children at Fajara, and found an average value of 22·5 units—a figure which is probably very near the equivalent of the Kampala value.

In a series of 8 children with " fatty liver disease " investigated in the West Indies, Waterlow (1948a) found an average level for alkaline phosphatase of 19·7 King-Armstrong units, but this was

nost exactly the same as the level he found (19·4 King-Armstrong
its) in a series of 14 other children who appeared to have no liver
mage. At Kampala, the average of 23 estimations was 11·8
ing-Armstrong units, which was below the normal range (15 to
units) quoted for children by Behrendt (1949). In Ceylon
ayasekera *et al.*, 1951), the average of 40 estimations was 15·8
ing-Armstrong units, and the values in children who died were
ghtly higher than in children who survived.

(*b*) *Duodenal enzymes.* Carvalho, Schmidt and Pinto (1947)
tubated 6 children during convalescence from kwashiorkor and
und that the amounts of trypsin and lipase in the duodenal juice
ere reduced, and Véghelyi (1948a, b) also found that pancreatic
zymes were affected. Lipase was reduced first, and afterwards
ypsin ; amylase survived considerably better, and never dis-
peared completely. Véghelyi said that the changes might occur
hough the serum proteins, and hepatic function, were apparently
rmal, and thought that inhibition of pancreatic activity was one
the early signs of protein deficiency.

Pancreatic enzymes were investigated at Kampala by Thompson
d Trowell (1952, see Table 15, p. 215), who found average maxi-
um values of 0·40 units amylase and 1·00 units lipase in 40 children
o had kwashiorkor, and an average level of 4·2 units trypsin in a
ther series of 6 children. Twenty-four children without signs
kwashiorkor had averages of 2·92 units amylase and 3·84 units
ase, and one similar child had 56 units trypsin. The reduction
e to the kwashiorkor therefore seemed to be very considerable in
ent. The coeval histological changes are described on p. 144.
nilar results have recently been reported from Mexico by Gomez,
lvan, Cravioto, Frenk and Vazquez (1953). They could find no
relation between the activity of the duodenal enzymes and either
state of the appetite or the level of the serum albumen.

Achar and Benjamin (1953) working in Madras, made qualitative
mations of tryptic activity in the stools of 7 children and the
denal contents of 18. In every case some activity was found,
the significance of this observation is a little doubtful. Quanti-
ve measurements would have been more valuable.

(*c*) *Tissue enzymes.* Reference has been made above to Water-
's (1950) findings of reduced activity of plasma pseudo-cholin-
rase in Fajara children. He also investigated the activity of
enzyme in liver tissue (Waterlow, 1950 ; 1951b). His results,

and those he obtained when he estimated the activity of cytochrome oxidase and lactic dehydrogenase, are summarized in Table 16 (p. 224). The cholinesterase was reduced, but the other enzymes did not seem to be affected. The importance of this finding is discussed elsewhere (p. 223). The number of children investigated by Waterlow was small, and the work should be repeated as soon as possible, and extended to cover other enzyme systems ; it should be extremely fruitful.

Sriramachari and Ramalingaswami (1953) were able to make qualitative estimations of the amount of alkaline phosphatase in liver biopsy tissue by using a histochemical method. They found that the activity of the enzyme was apparently increased in the acute stage of the disease. At first sight this finding seems to contradict the result of serum analysis (p. 169) ; it will be seen, however, that when treatment was begun, the activity of the serum enzyme fell (p. 211).

5. Tissue analysis

In view of the histological evidence (p. 128) for the deposition of fat in the liver in kwashiorkor it is of interest to know the percentage of fat found by chemical methods ; inspection of histological preparations is a notoriously unreliable means of quantitative estimation. In the livers of 5 children who had died from " fatty liver disease ", Waterlow (1948a) found that from 24·6 to 49·5 per cent of the wet weight was accounted for by fat. He estimated the phospholipid in three cases, but thought that the very low results he obtained might be artifacts, due to prolonged fixation of the tissues in formol. His determination of the iodine number of the fats in three cases showed no difference from that found in children whose livers were normal. Jayasekera *et al.* (1951) found the iodine number to be low in all the four cases they investigated.

The livers of 2 children who had died at Kampala in the acute stage of kwashiorkor were analysed by Professor A. C. Frazer. Parts of one liver were preserved in formol and in saline, but the analyses of both parts gave similar results. The total lipids accounted for about 12 per cent of the wet weight : the percentage composition of the lipids was 17·5 free fatty acid (as oleic acid), 2·5 cholesterol, 10·5 phospholipid (as lecithin) and 69·5 neutral fat. On a dry weight basis, 49 per cent of the other liver was lipids, the percentage composition being 35·0 free fatty acid, 2·4 cholesterol, 9·5 phospholipid and 53·1 neutral fat. Frazer's comment on these analyses was that the phospholipid was within normal limits, but hat the fatty acids and glycerides were grossly increased: the ormal figures for the two combined should be about one-third of he phospholipid. Ramalingaswami, Sriramachari and Tulpule 1952) found increased amounts of cholesterol (up to 10 per cent of he dry weight of the tissue in one case) in four livers from children ho had kwashiorkor, but did not find good correlation between the mount of cholesterol and the amount of fat.

Auffret and Tanguy (1950) analysed liver and muscle tissue of hildren who had died of kwashiorkor, and their results are shown n Table 5. The variations are rather large, and the results are not asy to interpret, but it seems without doubt that the total fat was of he same order as that found by Waterlow. The amounts of ethionine in liver and muscle proteins were said by Auffret and anguy to be identical with the amount they had found in the rmal individual, but their values are somewhat lower than those ven for mammalian muscle and liver by Block and Bolling (1951). n the other hand, recent experimental work on the whole suggests at in various states of undernutrition, the proteins of the liver do t undergo qualitative alteration, the ratio of S to N tending to main unchanged although the total protein may be reduced.

TABLE 5

Protein, methionine and fat in tissues of children dying from kwashiorkor

(*From Auffret and Tanguy*, 1950)

All values are for 100 g. tissue or protein.

ase No.	Age (years)	Water in liver g.	Fat in liver g.	Protein in liver g.	Methionine in liver g.	Methionine in liver protein g.	Protein in muscle g.	Methionine in muscle g.	Methionine in muscle protein g.
1	2	57·1	29·8	11·46	0·197	1·70	—	—	—
2	2	60·8	21·3	16·10	0·283	1·75	20·64	0·417	2·02
3	4	55·3	32·7	10·30	0·182	1·80	14·65	0·417	2·03
4	2	49·9	38·1	9·40	—	—	—	—	—
5	2	75·1	6·2	16·36	0·283	1·73	15·00	0·305	2·03
6	2	—	46·8	—	—	—	—	—	—
7	2	—	43·0	—	—	—	—	—	—

The analysis of liver biopsy tissue by Sriramachari and Ramalgaswami (1953) was not confined to alkaline phosphatase (p. 170). was found that in acute kwashiorkor there was a marked increase cholesterol—probably in the esterified form—and a considerable luction in the number of particles of nucleoprotein that could be monstrated in the liver cells. The appearances of the cells led also to the conclusion that there was no serious defect in their ability to form glycogen—a conclusion different from that of Holmes and Trowell (1948; see pp. 174 and 262), who investigated this function in one child and in adults.

Auffret and Tanguy said that the estimations of muscle were very difficult because so much fat was present. They also said that the findings resembled those in the experimental production of fatty livers by gavage; the liver is not one of the first organs to accumulate fat, when that procedure is used, but one of the last. There is no doubt that there is much to be learnt from the wider use of tissue analysis; it would be of value to know the extent to which the entire body is depleted of protein in kwashiorkor, and to know which organs are especially affected. Estimations of the amounts of choline and cholesterol in brain, suprarenal and other tissues should also be made. Samples of the home diets of the children should be analysed at the same time to see how much of these substances they contain.

6. Some other constituents of the serum

'Total lipoid' in serum was estimated by Van Der Sar (1951). In 11 of 16 children the values were higher than 620 mg./100 ml., which appears to be the normal level for children (Behrendt, 1949); values over 900 mg. were found in 5 children. 'Phospholipids' in serum were said by Carvalho (1947) to be at the low level of 6·1 mg./100 ml. It is of interest to note that a low level was also found in cases of hunger oedema by Bloem and Neumann (1953) and was believed by them to be one of the most important biochemical abnormalities occurring in that condition; they attributed it not to the general caloric deficiency of the diet but to lack of methionine, choline and lecithin.

Carvalho *et al.* (1945) reported average figures of 7·39 mg. calcium and 3·36 mg. phosphorus/100 ml. plasma, and Chaudhuri (1948) found that plasma chlorides ranged from 436 to 467 mg./100 ml. The normal ranges for calcium and phosphorus are 10·5 to 12·0 mg. and 4·7 to 5·6 mg./100 ml. respectively, and chlorides usually lie between 570 and 620 mg./100 ml. (Behrendt, 1949). A few estimations of sodium by Stransky and Dauis-Lawas (1950a) suggested that there might be slightly lowered values in kwashiorkor, but the same authors' results for potassium were so variable that no conclusions could be drawn. It seems likely that some at least

f these abnormal findings were influenced by states of water reten-
on or dehydration, and have therefore only limited significance.
lanafy (1948) found calcium values of the order of 9·0 mg./100 ml.
—that is, almost within the normal range—but said that tetany was
able to develop at the high level of 8·0 mg./100 ml.; it does not
sually occur, even in hypoparathyroidism, until the level is reduced
about 7·0 mg./100 ml.

The results obtained by Trowell, Moore and Sharman (in the
ress) for the analysis of sera for carotenoids and tocopherol are
iown in Table 6. The children with kwashiorkor had low levels,
ut the importance of this observation is doubtful. It may only
eflect part of the generalized failure in intestinal absorption.

TABLE 6

arotenoids and tocopherol in the serum of children in Mulago Hospital, Kampala

(*From Trowell, Moore and Sharman, in the press*)

	Number of children	Average age (months)	Carotenoids µg./100 ml. (mean and range)	Tocopherol mg./100 ml. (mean and range)
hildren with kwashiorkor	12	30	23 (4–54)	0·67 (0·35–1·06)
hildren without kwashiorkor	4	27	107 (46–142)	1·10 (0·85–1·40)

Tests of function

It was stated by Bergouniou and Trémolières (1952), who did
ot, however, appear to be writing from their own experience, that
l hepatic tests give abnormal results in kwashiorkor, and this was
rtly confirmed by Van Der Sar (1951), who performed the
omsulphthalein clearance test on 16 children, and found that only
of them cleared more than 10 per cent of the test dose. In the
tests that Waterlow (1948a) made, the clearance was usually much
gher, and he thought that the test was of value only to indicate the
verity of the condition; if the result was very strongly positive
e prognosis was bad. Jayasekera *et al.* (1951) thought the
st was valuable. The serum bilirubin was raised in the more
vere of Waterlow's and Jayasekera's cases, but the highest value
und by Waterlow was only 1·8 mg./100 ml., which is below the
vel at which jaundice normally becomes apparent. In the most
vere of Jayasekera's cases, values up to 2·73 mg./100 ml. were
und. Alkaline phosphatase estimations (see above, p. 168 and
o p. 211) are sometimes used as tests of liver function, but the
sults are difficult to interpret as the level may be raised if the liver

is damaged, and depressed if there has been a caloric deficiency in the diet (Sherlock and Walshe, 1951).

Niemeyer and Meneghello (1950) employed a whole battery of flocculation tests—colloidal gold, scarlet red, thymol turbidity and cephalin-cholesterol—but could find no correlation between the results of the tests and either the clinical condition of the children or the amount of liver fat. Véghelyi (1950a), however, thought that Takata-Ara, Weltmann and cephalin flocculation tests tended to give positive results in the more advanced of his cases. Van Der Sar (1951) found the cephalin flocculation and Takata-Ara tests were usually negative; Ballabriga (1950) found the Takata-Ara tests only rarely positive, but the cadmium test constantly and strongly positive (and offering an important guide to prognosis) in severely ill children. The Weltmann test was also positive, and the nephelogram showed a marked shift to the left, in Ballabriga's children. All these tests probably depend on serum globulin, and especially on the γ-fraction. Gomez, Galvan, Bienvenu and Muñoz (1950) performed Van den Bergh, bromsulphthalein, cephalin-cholesterol and thymol tests on a group of malnourished children. The cephalin-cholesterol and thymol tests gave some abnormal results, but these were attributed to infection, or processes of regeneration in the liver, rather than malnutrition.

Chaudhuri (1948) reported fasting blood sugar levels that lay between 60 and 80 mg./100 ml. He gave 30 g. glucose by mouth to some of his patients, and found that the maximum blood level was reached after 45 minutes, but that this level was only 95 to 133 mg./100 ml. At the end of 3 hours the level fell, to between 80 and 105 mg./100 ml. He decided that the response was suggestive of hepatic insufficiency, but it might equally well have denoted defective absorption from the gut. Measurements of the rise in blood sugar after giving a known amount of glucose by duodenal intubation would give useful information. Niemeyer and Meneghello (1950) gave dextrose and galactose intravenously and found 5 of 12 children had a decreased tolerance of glucose, and 2 of 11 had a decreased tolerance of galactose; the altered tolerance seemed to bear no relation to the degree of fatty infiltration of the liver. The ability of the liver to form glycogen from glucose was measured in one child by Holmes and Trowell (1948) and was found to be reduced.

According to Bergouniou and Trémolières (1952) phenolsulphonephthalein excretion is slightly retarded in kwashiorkor. There s little other evidence of abnormal kidney function, but the albuminuria (p. 105) and the high urea levels occasionally found in onvalescent children (p. 210) may denote some degree of failure.

Waterlow (1948a) investigated the gastric acidity of a few childen, and found that it was not impaired. Test meals were given to children by Jayasekera *et al.* (1951), and Table 7 provides a sumnary of the results; the amount of free acid was very small, and he total acidity was low. On the other hand, the peptic activity id not seem to be much affected—a finding which, taken in conction with the results of the fat balances shown in Table 8 . 176), suggests that the digestive powers of the children were eater than is usual in kwashiorkor. The children who died were id not to show pancreatic atrophy.

TABLE 7

esults of giving gastric test meals to children in Ceylon suffering from kwashiorkor

(*From Jayasekera et al.*, 1951)

	Free acid (ml. N/10 HCl/100 ml.)			Total acid (ml. N/10 HCl/100 ml.)			Peptic activity (units)		
	At start	After 30 min.	After 60 min.	At start	After 30 min.	After 60 min.	At start	After 30 min.	After 60 min.
Children who died	0	0	0	1·2	7·3	8·6	7·6	7·2	20·9
	0	0	46·0	18·1	37·5	75·6	19·3	19·6	3·7
	0	0	0	2·9	3·8	7·6	23·7	13·9	19·7
Children who survived	0	0	2·4	2·5	8·7	15·6	23·0	20·9	31·1
	0	0	0	6·2	17·5	20·0	18·9	27·1	22·8
	0	0	0	3·6	7·5	13·3	13·7	13·9	36·5
	0	0	0	2·5	10·0	4·6	40·0	19·1	35·6
	0	3·5	4·5	5·0	9·8	10·3	18·9	36·1	10·7

The methods used, and the unit of peptic activity, are explained by the authors.

Steatorrhoea

There have been few well-founded reports of excess fat in the ools, although several writers have said that it may have been esent. Van Der Sar (1951) stated that most of his patients had atorrhoea. The mean total fat was determined in 19 cases. In o specimens the faecal fat was more than 60 per cent of the dry ight of the faeces, in three it was between 50 and 60 per cent, four between 40 and 50 per cent, in six between 30 and 40 per nt, and in only two was it between 10 and 20 per cent, which is

TABLE 8

Results of analysis of the fat in faeces and blood of children in Ceylon
(*From Jayasekera et al.*, 1951)

	Number of children	Percentage of fat in faeces	Percentage of fat present as soaps	Percentage of fat present as fatty acids	Percentage of fat present as neutral fats	Blood fat mg./100 ml
Children with kwashiorkor who died	13	*36·9*	*33·9*	*47·4*	*24·6*	*5103*
Children with kwashiorkor who survived	27	*27·2*	40·0	36·6	18·9	2250
Children without kwashiorkor	50	10·0	46·4	37·7	15·9	1740

The results for the children with kwashiorkor which are significantly different according to statistical analysis, from those for the normal children, have bee printed in italics.

regarded as the normal percentage. There was a rough correlatio between the percentage of fat in the stools and the lipaemia (p. 172)

A moderate degree of steatorrhoea has been found fairly consistently at Kampala by Thompson (unpublished results), and on child given a milk diet absorbed only 50 per cent of the fat. A fev other fat balances have been carried out there (Dean, 1952 *Proc.* a)

TA

Results of biochemical investigation of childre
(*From Dricot, Be*

		Serum components (values for 100 ml. serum)									
Child	Age in years	Total protein g.	Albumen g.	Globulin			A/G ratio	Ca mg.	Inorganic P. mg.	Total cholesterol mg.	To lip g
				α g.	β g.	γ g.					
Mid	15	4·27	0·27	0·90	0·84	2·25	0·07	7·49	2·50	75	1·
Nzu	12	5·08	0·99	0·66	1·32	2·12	0·24	7·88	4·80	138	1·
Nio	7	3·88	0·69	0·72	1·00	1·46	0·21	7·39	2·90	155	1·
Man	10	6·58	1·97	1·54	0·78	2·29	0·42	9·06	3·90	213	2·
Min	8	5·71	1·79	0·86	1·15	1·90	0·46	9·26	3·60	150	2·
Mbu	8	5·16	1·83	1·14	0·62	1·56	0·55	8·47	4·00	98	2·
Kak	6	4·10	0·85	0·66	1·10	1·54	0·24	7·58	4·60	121	1·
Ani	15	4·97	1·32	0·92	0·94	1·79	0·36	8·57	4·35	155	1·
Normal values quoted		7·01	3·77	1·10	0·94	1·20	1·16	9·0–11·5	5·0–5·5	150–200	0·4

The fractionization of the serum proteins was carried out by the method of Wolfson, Cohn, Carvary and Ichaba (1948). Details of this and the other methods employed are given by Dricot *et al.*

uring one of these, in which the subject was given a diet of soya nd banana containing about 24 g. fat each day, the absorption of t was 86 per cent (see Table 10, p. 200). Jayasekera *et al.* (1951) so investigated the fat balance in several cases, but came to the nclusion that there was little correlation between the percentage fat in the faeces and the severity of the general condition.

Further results obtained by the same authors when they analysed eces are summarized in Table 8. The fatal cases are the most vealing; the total fat accounted for nearly 37 per cent of the dry eight, and 47 per cent of the fat was in the form of fatty acids. s in Van Der Sar's cases, the fat in the faeces was apparently correlated with the degree of lipaemia.

Analysis of urine

Urines were collected over 24-hour periods from a few of the ys in the series of cases reported by Jayasekera *et al.* (1951). The mber of boys is not stated. The results, when compared with sults of analyses of urines from children who were not ill, showed a nsiderable reduction in the total nitrogen excretion and in the excreon of creatine. The excretions of creatinine appeared to be normal.

go (Belgian Congo), aged 6 to 15 years
harles, 1951)

			Functional tests						
10-	Amylase (Somogyi) units	Alkaline phosphatase (Bodansky) units	Takata-Ara test *	Thymol test units	Distilled water test units	Indirect bilirubin test mg. %	Hippuric acid test Elimination %	Phenolsulphonephthalein Elimination † %
	90	9·5	++++	9·5	4·9	0·4	—	—
	79	8·3	+++	5·9	10·5	0·3	—	—
	85	14·5	++	4·7	8·2	0·3	28	36
	196	15·7	++	5·9	0·6	0·3	57	71
	179	2·9	++	6·0	0·7	0·4	79	75
	228	4·8	+	3·5	1·2	0·5	54	68
	180	2·2	++	4·0	1·7	0·1	54	63
	114	10·0	++	5·2	13·0	0·7	34	41
	85–150	5·0–12·0	0	0–4·0	—	0·2–0·8	80	40–50
0								

linical condition: All except Man had some alterations of the skin; all altered hair; the liver was enlarged except in Nzu, N10 and Kak; Nzu Man had no oedema, but all the others had oedema and it was gross in N10. Min and Mbu were twins. * After 30 min. † After 70 min.

10. Biochemical investigation of older children

All that has been said so far in this chapter relates to children in the first few years of life. A careful study, containing much detail, was made by Dricot, Beheyt and Charles (1951) of a small group of children aged 6 to 15 years from the district of Kwango, in the Belgian Congo. Some of the results obtained by serum analysis are shown in Table 9. The important findings seem to be a reduction of the total serum proteins, caused chiefly by a fall in albumen (giving a low ablumen/globulin ratio), low calcium and phosphorus, high total lipids (all the sera were said to be milky) and a low percentage elimination of hippuric acid. Compared with the findings in the Kampala series of Dean and Schwartz (1953) the average total protein level was somewhat higher in the Kwango children, the albumen/globulin ratio lower (even when allowance is made for the difference in methods), and the level of amylase was constantly higher. The level of alkaline phosphatase (expressed in Bodansky units by Dricot *et al.*) showed great variations from case to case, but the flocculation reactions were usually positive.

Amongst other findings of interest there was albuminuria (in 7 of 8 of the children), no galactosuria after injecting amounts of the sugar ranging from 11 to 40 g., and normal excretions of phenolsulphonephthalein, but oliguria in the first days of treatment. One child had a urinary infection. Estimations of the activity of duodenal enzymes in 4 children showed a reduction of lipase in all 4, but a reduction of trypsin in only 1.

THE TREATMENT OF KWASHIORKOR

Until the nature of kwashiorkor was understood, it was difficult to find a logical foundation for treatment. Gillan (1934–35) was reduced to treating his children as for enteritis, promoting their perspiration and maintaining their nutrition with foods, such as glucose, which he thought they could most easily absorb. This was, of course, merely symptomatic treatment. The use of a mercurial diuretic by Russell (1946) and novocaine by Delon (1951), which were said to reduce the oedema in a few cases; comes into the same category, and so does the use of carob bean (Bergouniou and Trémolières, 1952) or of any other medicament which aims at the control of the diarrhoea, or of some other symptom, without affecting the underlying cause. Treatment of this kind may sometimes be a luable temporary measure, as Waterlow (1948a) pointed out, but n be of no permanent value.

Vitamin therapy

The pellagrous nature of certain of the skin lesions (p. 83) aturally led to attempts to cure the whole condition with nicotinic cid. Trowell (1941–42a), Gillman and Gillman (1945a), and ughes (1945–46) thought this vitamin of little value or even harml, and some writers (for example Bergouniou and Trémolières, 952) have pointed out that it may be dangerous because it utilizes ethyl groups which would otherwise be free for more vital synetic processes. Others (for example Kark, 1943) thought that cotinic acid improved the skin, but Hughes (1945–46) found it to without specific effect on either the skin or the diarrhoea.

Other members of the vitamin B complex have also been used treatment with and without nicotinic acid. Riboflavin appeared Kark (1943) and Hughes (1945–46) to help in curing the skin, but illman and Gillman (1945a) thought it of little value. When boflavin, nicotinic acid, thiamine, brewer's yeast, vitamin A and tamin D were added to various diets the effects were found gularly to be deleterious (Gillman and Gillman, 1946). Hanafy 948) used the whole vitamin B complex to combat anorexia. lark (1951a) agreed with an earlier dictum of Trowell's advising gainst the use of any vitamin therapy. This was sound in so far it directed attention away from vitamin deficiencies as the prime use of the disease, but the occasional success reported with vitamin eatment might be regarded as an indication of the possibility that e disease may occur in conjunction with vitamin deficiencies, or at such deficiencies may arise as a terminal event in children who ave been subjected to a long period of metabolic disturbance. An sociation with vitamin deficiency is much more likely in a country here pellagra is common, such as South Africa, than it is in Uganda, here pellagra is rare. One point of view in regard to vitamin erapy is shown by Flores (1947), who advocated very large doses of y vitamins thought necessary, saying that the large doses were quired because absorption was poor. With modern injection erapy, he would presumably moderate his dosage. Another ntral American paediatrician (Gomez, 1953, personal communican) does not consider that vitamins play any considerable part in ccessful treatment.

Frontali (1953) found that he could abolish slight irregulariti in the electrocardiogram (p. 101) by giving thiamine. The dipho phate (cocarboxylase) produced the most rapid results and w therefore used before any intravenous therapy was attempted, tl object being to lessen the danger of the transfusions by avoiding tl overloading of the circulation.

Various reasons, which must include the humane necessity fc the immediate rescue of the children from a dangerous conditio seem usually to have prevented the trial of any one therapeut agent at a time. This is true, not only of the vitamins but also the other substances which have been used in treatment, and it often impossible to decide, on the evidence given, which of the mar possibly advantageous therapeutic agents offered simultaneous has been the one actually responsible for improvement. Tl difficulty is increased when a substance is given that may be effecti through one or more of its ingredients, especially if the substance known to be capable under normal circumstances of being split the body into those ingredients. An example is whole liver. contains all the ordinary members of the vitamin B complex, an folic acid and vitamin B_{12}, as well as choline and cholesterol ; it als provides protein and therefore amino acids. For the rest of th chapter, treatment will be considered under the headings o materials which can be looked on primarily as supplying the lipotrophic factors methionine, choline and vitamin B_{12}, and thos supplying total protein.

2. Lipotrophic factors

It may be advisable to attempt a definition of these factors Much of the literature was collected by Wahi (1947) and a brief bu authoritative summary was made by Best (1950). Abnorma deposition of fat, especially in the liver, can be produced by variou means. Amongst these means are poisons such as carbon tetra chloride and phosphorus, and the processes of anoxia and anaemia the absorption of toxins from severe burns may have a similar effec (Gelfand, 1946). An excess of dietary fat, if sufficiently long continued, may give rise to a relative deficiency of choline, whicl may lead to fatty infiltration, and choline deficiency may be brough about if any of the materials required for its synthesis—for example methionine—are not available. This might happen if the break n of protein was imperfect through such causes as inadequate creatic function.

The tendency towards fatty infiltration, and in some cases even established infiltration itself, can be reduced or abolished, as nt be expected, by choline or methionine, which are therefore ied 'lipotrophic'. In recent years vitamin B_{12} has been placed ne same category. It is perhaps more accurate to say that the min and the substances usually found allied to it should together alled lipotrophic, because pure crystalline vitamin B_{12} may be fective (McCormick and Drill, 1950). There is a connection, ch has not yet been fully worked out, between methionine and min B_{12} (Zucker and Zucker, 1950). The vitamin may have a aring' action, possibly by increasing the efficiency with which amino acid is utilized or synthesized (Oginsky, 1950). It cannot ace the amino acid, and neither can it replace choline, in the of rats; if those diets already contain enough choline, its ition causes no acceleration in the rate of growth. It is believed lay a part in the synthesis of choline, of nucleic acids and possibly aemin (Stekol, Weiss and Weiss, 1952).

The recognition of the importance of vitamin B_{12} was delayed ause it was not realized that the vitamin could be stored by the her and passed on in her milk. This has been established for rat (Zucker and Zucker, 1950), in which species the extent of maternal stores may decide whether or not a deficient diet given he weanling produces fatty infiltration of the liver and other damage (Dean, to be published).

The importance of this digression lies in the fact that all the tances which have been reported with any constancy to cure shiorkor have in common that they are sources not merely of ein, and therefore of methionine, but also of vitamin B_{12}. Some hem also contain considerable amounts of choline.

he use of lipotrophic factors in treatment

a) *Hog's stomach.* Preparations of hog's stomach, under various rietary names, have been claimed to cure kwashiorkor. The reports came from Gillman and Gillman (1945a). In their s, hog's stomach was brilliantly successful, 'clinically mori-' patients recovering in 7 to 14 days on a daily dosage of of a desiccated commercial preparation, given on 5 days in ion to a diet which was not specified, but was thought to be ideal for the age and weight of the child. In a later accou (Gillman and Gillman, 1946) the same authors said they had treat 50 cases with a mortality of only 6 per cent, but that a combinati of hog's stomach, aneurin, and riboflavin, with iron, was conside ably less effective, the mortality rising to 35 per cent in a series 20 cases. They did not consider that their good results were d to the choline that the preparation contained. Hanafy (1948) al said that hog's stomach (but not ox's stomach) was useful in trea ment, although he seems to have preferred crude liver—a treatme recommended by Russell (1946); a crude liver extract used Gillman and Gillman (1946) gave poor results, especially when th vitamin mixture was added, and Carvalho *et al.* (1945) also report the failure of a liver extract. An extract used by Chaudhuri (194 was apparently helpful.

The good results obtained by the Gillmans led to attempts repetition by several other workers. There was consistent di appointment. Trowell and Muwazi (1945) thought that their fir few cases showed some improvement, but that may have been part due to the milk that the children were also receiving. Gelfa (1946), Waterlow (1948a), Pieraerts (1949a), Meneghello *et al.* (194 and Janssen and le Roux (1950a) all reported unfavourably, and did Altmann (1948), who suggested that any good effects the hog stomach might have shown in the Gillmans' hands were probab due to the protein it contained. There are a number of possib explanations for the failure. The preparations used by the vario authors were of several different makes, and were not fully sta dardized. They may therefore have contained different amounts choline, protein and vitamin B_{12}—the existence of the last nam not being known when most of the experiments were performe Different preparations of hog's stomach undoubtedly contain wide different amounts of the vitamin. Even so, it is curious that t Gillmans alone should have had any important success.

(*b*) *Choline.* Under this heading can be included not mere the pure substance but the pancreatic preparation lipocaic, which h been shown to be lipotrophic by virtue of its choline (Wick, 194 and pancreas itself.

Waterlow (1948a) gave 0·5 g. choline and 1·0 g. inositol (anoth lipotrophic substance) to 3 children who were also being given cow milk. Two of the children, who were extremely ill when the trea ment began, died in 2 and 4 days; the third survived, but the val

the choline and inositol, which were given for 7 days, was con-
dered doubtful. Trowell (1948–49), who gave 2·0 g. choline daily,
ought it had slight lipotrophic activity, judging by liver biopsy;
e children were also being treated with milk. Meneghello and
iemeyer (1950) used choline hydrochloride (5·0 g. daily) with a
gh protein diet based on skimmed milk. Twenty-three children
ıd this combination, and were compared with another 18 children
ven the milk without the choline. Serial biopsies of the livers
dicated that the choline accelerated the removal of the fat although
e clinical course was not much affected.

Carvalho *et al.* (1945) gave lipocaic to 17 children in addition to
ied skimmed milk; all the children survived, but results almost
good were obtained in another group who had the dried milk
one.

One child who was fed on raw minced pancreas by stomach tube
Gillman and Gillman (1945b) made a slow recovery.

(*c*) *Methionine.* Gillman and Gillman (1945b) gave one child
0 g. methionine over 4 days and another 11·0 g. over 7 days, in
dition to what was described as a high carbohydrate diet, con-
ting of maize porridge and half-strength milk. They concluded
om serial liver biopsies that under these conditions methionine
d not remove fat from the liver. Waterlow (1948a) gave 5·0 g.
ethionine daily for 7 days to a child who was receiving 9·5 g. milk
otein. The child, who was not oedematous, lost weight and the
um protein did not improve, remaining about 5·2 g. 100 ml.
other child, who was receiving 38 g. milk protein, was also given
g. methionine daily for a week. There was some improvement
general condition, but it could not be claimed that the methionine
s responsible. Both of these children had enlarged livers; they
fered in this respect, therefore, from children with kwashiorkor
n in Uganda and elsewhere (see p. 99). Waterlow also gave
thionine to a third child, whose liver was not excessively fatty
had an early cirrhosis. Again there was no benefit, and the
eral conclusion was that methionine was of little value. Dricot,
neyt and Charles (1951) gave 2·0 g. methionine a day to one child
3 weeks and for an unspecified period to another, but without
iceable effect. Both children were receiving skimmed milk.

In summarizing the results of various treatments, Waterlow
phasized that assays of the therapeutic effectiveness of different
stances should be made at equal levels of protein intake. Ideally

the protein intake should be no more than that required to maintain the child's condition without either improvement or deterioration, and if an amino acid such as methionine is being given, the amount present in the rest of the diet should be accurately known. If possible, the amount should be so small that an addition might be expected to produce a large effect. Also, the diet should not include any other lipotrophic substance. So far, no trials have been carried out that satisfy these requirements, but at Kampala 2 children were given a banana diet which, although it has not yet been fully analysed, is believed to contain very little methionine or choline. The diet provided about 10 g. protein daily. When it was supplemented with *dl*-methionine, of which 5·0 g. was given daily for 7 days, there was no marked improvement in the clinical condition or the serum chemistry of the children. For various reasons, the experiments were not considered entirely satisfactory, and they should be repeated with full analyses of the diets. It was fairly clear that the methionine alone could not bring about the cure of the children, but the question of the relationship of the methionine to the rest of the diet, and to the total protein intake, needs to be considered more carefully than has so far been done. It is probably unsound to expect to show any improvement in children who are suffering from kwashiorkor if the rest of the diet is inadequate to support the methionine.

A further series of 8 children, who were being given a diet of soya and banana, with a vitamin mixture that included vitamin B_{12}—a diet that provided a total of about 50 g. protein, with just under 2·0 g. methionine—were given an additional 5·0 g. *dl*-methionine daily for periods between 2 and 21 days. The methionine caused some anorexia, and the full amount was not taken every day. The methionine did not appear to be beneficial in any way (Thompson, unpublished).

High-protein diets such as those which have been used successfully at Mulago (see p. 190) probably contain no more than 1·7 g. methionine, and it may be that this amount is all that is needed, provided that adequate amounts of vitamin B_{12} and choline are also present in the diet. The minimum amount required is unknown, and its determination would obviously be a highly complicated problem.

Treatment with protein hydrolysates, human serum, plasma and blood

For the treatment of a condition in which, for a long time, almost ne only known biochemical change was a lowering of the serum pro- eins, it was inevitable that hydrolysed proteins, and concentrated uman serum or plasma, should receive early trial. Treatment will ne day be carried out with mixtures of pure amino acids, but the cids have only recently become easily available in large quantities, nd they are still extremely expensive. The delay in their use is erhaps not so serious as might be thought at first: much of the arly work done with synthetic diets has been vitiated by the dis- overy of the importance of vitamin B_{12}.

Protein hydrolysates have been disappointing. Gillman and illman (1946), probably handicapped by the imperfections of the est hydrolysates known at the time--there were pyrexial episodes hat might nowadays have been avoided—were dissatisfied with their esults. They used 'a local casein digest', 'a whale-meat digest' nd 'an enzymatic digest of casein': all were given by mouth in ddition to what was thought an adequate diet, but many of the hildren who received the digests died. It was unfortunate that the est of the diet was not recorded. Without this information, no pinion can be offered as to whether or not the digests were ade- uately supported. A rich source of 'animal protein factor' might ave been of great value, although its use must have complicated e interpretation of the results. Enzyme-digested whale meat was id by Altmann (1948) to have been used successfully in "malignant alnutrition" by workers in Natal.

Pieraerts (1950b) used the proprietary brand of protein hydroly- te called Amigen, but it was useless in the treatment of five severe ses and did not compare favourably with milk in two slight cases.

Some workers (Trowell, 1948-49; Pagola, 1948; Chaudhuri, 48; Van Der Sar, 1951) have given small blood transfusions as rt of their treatment, but the amount of benefit due to the trans- sions cannot be assessed. Oomen (1951) used intraperitoneal nsfusions of whole blood in desperate cases where dietary treat- ent was thought to be impossible. He considered that blood ve better results than plasma. Pieraerts (1949b), one of the few vestigators who made a systematic trial of various treatments, found at he had most success with serum given subcutaneously. One hundred millilitres were given at a time, sometimes on consecutive days, and usually after a total of 500 ml. had been given there was a dramatic improvement. Although most of the children were being given milk at the same time, one child was treated with the serum alone, and survived. This led Pieraerts to the conclusion that in the very acute stage of the disease milk was probably not as valuable as the serum, because it could not be properly digested and absorbed —functions which he recognized to be poorly performed in kwashiorkor. The protein of the serum might be more readily available for synthetic processes in the body than the milk proteins ; it might also, he thought, be providing some substance of exceptional value in the treatment of kwashiorkor, but he could not say what that substance might be.

Achar (1950) was apparently able to use transfusions of blood and concentrated serum successfully when other treatments had failed, and repeated small blood transfusions have for many years been considered of value in treatment by workers in Central America (Cofiño Ubico and Klée, 1942 ; Flores, 1947 ; Autret and Behar, 1954) but Janssen and le Roux (1950a) found that it was useless and even dangerous to give blood, serum or saline intravenously, and came to the same conclusion about protein hydrolysates given in this way.

It has been the experience at Kampala that children with kwashiorkor, especially when they are in the oedematous state, tolerate intravenous transfusions poorly, and such transfusions are avoided as far as possible. Although little is known about the state of the various mechanisms which should be controlling water balance, it is quite clear that the balance is easily upset and that harm is done very easily. Stransky and Dauis-Lawas (1950a) would not, it seems, agree. They expressed the opinion that " there cannot be any proper treatment of hypoproteinaemia without parenteral administration of amino acids ".

5. Treatment with cow's milk

There is no doubt that the food which has been used most extensively in the treatment of kwashiorkor is cow's milk. It has, however, sometimes been reported (for example, by Achar, 1950), and it has been found at Kampala, that unmodified full-cream milk is badly tolerated—a fact which discouraged some of the early

orkers from using milk. Intolerance of fat was eventually
cognized to be partly responsible, and the intolerance is likely to
ecome obvious in tropical countries where the percentage of milk
t is often extraordinarily high : it may be more than twice that
the milk of European cows.

It has been found, however, that there is also an intolerance of
rbohydrate in severe kwashiorkor. Even skimmed milk may give
se to gastro-intestinal upsets. Dricot, Beheyt and Charles (1951),
though they gave skimmed milk cautiously to their patients, found
at it regularly produced diarrhoea which had to be treated with
rob flour. The diarrhoea was probably due to the intolerance of
rbohydrate which is found in severe kwashiorkor. The capacity
deal with the lactose of milk is restricted, most children being
nable to take more than about 70 g., the amount present in about
0 g. dried skimmed milk. The intolerance is not confined to
ctose, but extends to other sugars, and therefore presents an
vkward problem in treatment.

Skimmed, or partly skimmed, milk is obviously to be preferred
full-cream milk in the treatment of kwashiorkor. Skimmed milk
ntains about 4·5 per cent protein, and various devices have been
sed to increase the percentage. Janssen and le Roux (1950a)
nployed a mixture of 500 ml. peptonized milk, 5 level tablespoons
calcium caseinate, 2 tablespoons of sucrose and 3 tablespoons of
ctose ; to this was added 500 ml. of a 5 per cent solution of Amigen
5 per cent dextrose. In the heat of summer the Amigen tended
hasten the acid fermentation of the milk, and an alternative
ixture was made from unaltered skimmed milk and the calcium
seinate. On the average, the children received nearly 8·0 g.
otein, and 100 calories, for each kilogramme of their body weight.
the children were seriously ill, or anorexic, the feeds were given
gastric drip—a method which has been found effective in
e Belgian Congo (Demaeyer, 1952, personal communication).
sually, 300 to 500 ml. of the feeds were tolerated well in the first
hours, and the amount could afterwards be increased gradually.
fter 4 to 7 days, according to the condition of the child, minced
eat or liver, mashed vegetables, custards, fruit and biscuits were
troduced into the diet, the milk drinks still being given twice
ily. On these diets, 13 out of 51 children died, but 6 deaths
y have been due to other disease complicating the kwashiorkor.
e results were somewhat better than those obtained by feeding

another group of 50 children on a mixed diet which included dried hog's stomach, skimmed milk, minced meat and liver, vegetable soups and mashed potatoes, liver extract, iron, folic acid and various vitamins.

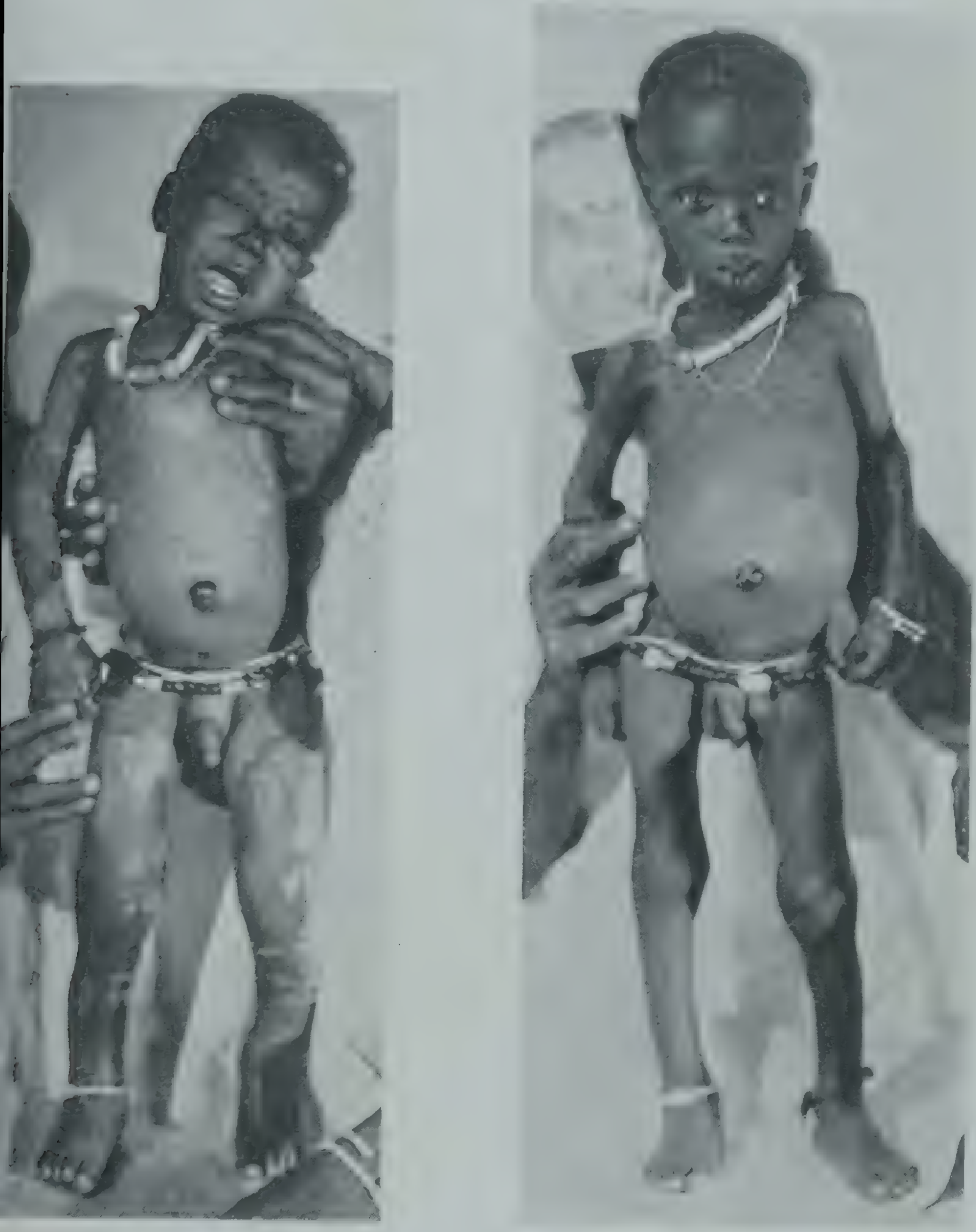
Wills (1951) was remarkably successful in her use of skimmed milk modified by the addition of previously soured cream, only one out of 32 children dying. (Deaths that occurred within 24 hours of the children's admission to hospital have been omitted.) Dr. Wills kindly provided the following details of preparation in a personal communication.

"At 4 a.m. 4 oz. of fresh cream are put in a cup which stands in hot water; four hours later 2 oz. of machine-skimmed cow's milk are added to this cream, the surrounding water still being kept warm. Eight hours later two more ounces of skimmed milk are added to the 'culture' and this is allowed to stand for a further 16 hours. Then the contents are added to 2 gallons of skimmed milk and are stirred in well and left to stand a further 24 hours when it is offered for the first time as 'Maas'."

The Maas had 3 per cent protein and provided 35 calories/100 g. Most children received 2·5 to 3·0 g. protein/kg. body weight daily. Achar (1950) obtained his best results with half-cream milk, acidified and fortified with casein products. The amount of fat was increased as the child's condition improved.

Dried skimmed milk is a convenient preparation, especially for the Tropics, and it is cheap in comparison with many other forms of high-protein foods. It was used by Altmann (1948), one part of the powder being added to ten parts of warm water, with some dextri-maltose. Ten drops of lactic acid B.P. were added slowly to each 100 ml. of the mixture; the addition had to be made slowly to prevent curdling. Small amounts of the feeds (150 to 300 ml.) were given in the first few days, and if more fluid was required, it was given as boiled water to the oedematous children, and as half-strength saline to those who were not oedematous. The amount of the mixture was increased gradually, it being the aim to give 3·5 g. protein and 75 calories/kg. body weight. Cereal gruels (10 per cent cereal in reconstituted dried milk) were added as the children recovered. The death rate was 20 per cent in a series of 30 cases. The average length of treatment in successful cases was 39 days. Van Der Sar (1951) also used a dried preparation. It contained skimmed milk and whole-milk curd, acidified with lactic id. Used in conjunction with repeated small blood transfusions, was so successful that only one out of 30 children died.

Senecal (1953, private communication) has recently reported



(*a*) (*b*)

20.—Treatment of kwashiorkor with a mixture of dried skimmed milk and a protein hydrolysate, providing 30 to 35 g. total protein (N × 6·25) daily. A case from Dakar, French West Africa, under Professor Jean Senecal.

a) Photograph taken 13th February, 1953. Note especially the misery, the eralized oedema and the widespread dermatosis.

b) Photograph taken 2nd March, 1953. The oedema has been lost and the has healed after very extensive desquamation.

ases described by Jelliffe (1952) at Ibadan were also remarkable for the extent he desquamation.

excellent results obtained by using a mixture of dried skimme milk and a proprietary protein hydrolysate. The mixture provide the equivalent of 30 to 35 g. protein daily and was given if necessa by gavage. Twenty of 22 children made good recoveries. Th other two, who were very ill, died because the feeding tube w passed into the trachea—an accident which, as Senecal said, n only emphasizes the need for an improvement in the skill of Africa nurses, but is an indication of the extreme feebleness of the chi with acute kwashiorkor. Photographs of a child who was succes fully treated are reproduced in Fig. 20.

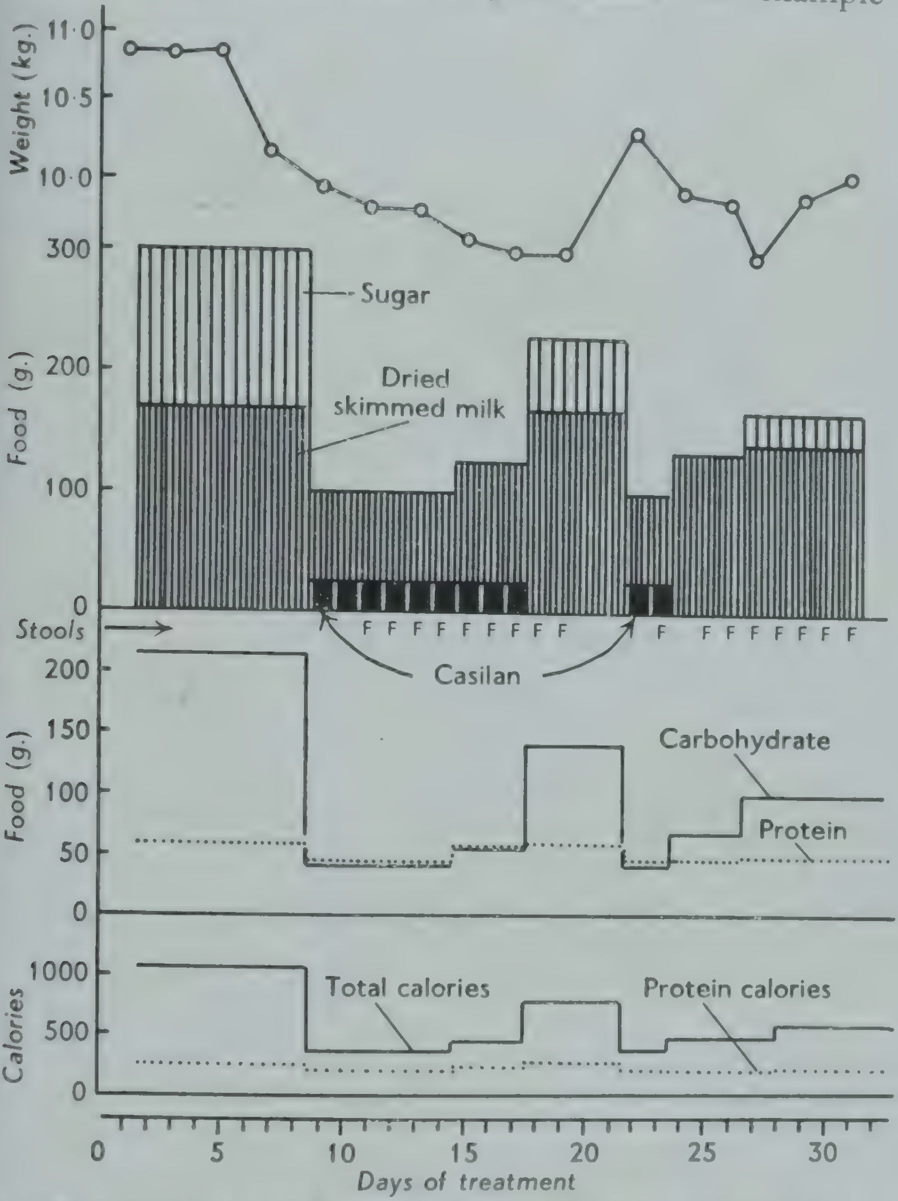
Skimmed milk powder has also been used at Kampala, and or scheme of treatment was described as follows (Trowell and Dea 1952).

" The day of the child's admission to hospital serves as an observa tion period, and during that time nothing is allowed except freque drinks of glucose water. The next day feeding with dried skimme milk is begun. Usually, for a child about 2 years old, 4 ounces the dried milk are mixed with 2 pints of 5 per cent glucose wate or with 2 pints of water and an ounce of sucrose. Six feeds, eac of 4–6 ounces, are given at 3-hourly intervals during the day. Th child is left undisturbed during the night as far as possible. the general condition of the child, and the nature of the stools, sho that this diet is being well tolerated, the concentration and amou of the skimmed milk mixture are gradually increased, a period 3–4 days being taken over each step forward.

" If there is persistent diarrhoea, the diet is changed to a mixtu of a high-protein preparation and skimmed milk. For the mos certain effect, the amounts of milk protein and carbohydrate shoul be approximately equal. This can be achieved by giving, f instance, 2 ounces of a proprietary milk-casein preparation (contai ing 80 per cent protein) and 4 ounces dried skimmed milk, mixe with sugar water to provide the usual 4–6 ounce feeds. Th diarrhoea should stop within 2 days, and if it does not, some reaso other than defective digestion and absorption should be suspecte The amount of skimmed milk is increased, and that of the high protein preparation is decreased, in carefully observed steps, unt nothing but skimmed milk is being given.

" After the stools have remained well formed for a period 4–5 days, a cereal porridge is added to the diet. This porridge made by taking 4 ounces finely ground maize flour, 2 ounces skimme lk powder and 1 ounce sugar. Water is added, and it is cooked a double saucepan for several hours until the starch grains are t and the final weight is 12 ounces. The porridge is given twice lay, in 6-ounce helpings. If the porridge is well tolerated, other -free foods, such as cooked banana or rice, are included in the et. Finally, the porridge is made with full cream dried milk, d a full diet is allowed."

At the time when this scheme was introduced, it was not realized t intolerance of lactose was likely to occur. An example of the



21.—Treatment of kwashiorkor with dried milk, and Casilan, a calcium aseinate preparation. The amount of protein was kept approximately the same throughout, and the amount of carbohydrate was varied. The stools vere formed (indicated by F) when the amount of carbohydrate was small. he rise in weight after the twentieth day was probably due to the increase in ies. It was not maintained when the stools deteriorated.

use of the treatment is shown in Fig. 21. The child was given first 170 g. dried skimmed milk, which yielded 50 g. protein, wi some glucose. After about 5 days, oedema began to be lost, b the stools remained loose. On the seventh day the amount skimmed milk was reduced but the total protein was kept consta by the addition of the concentrated milk protein preparation. Th

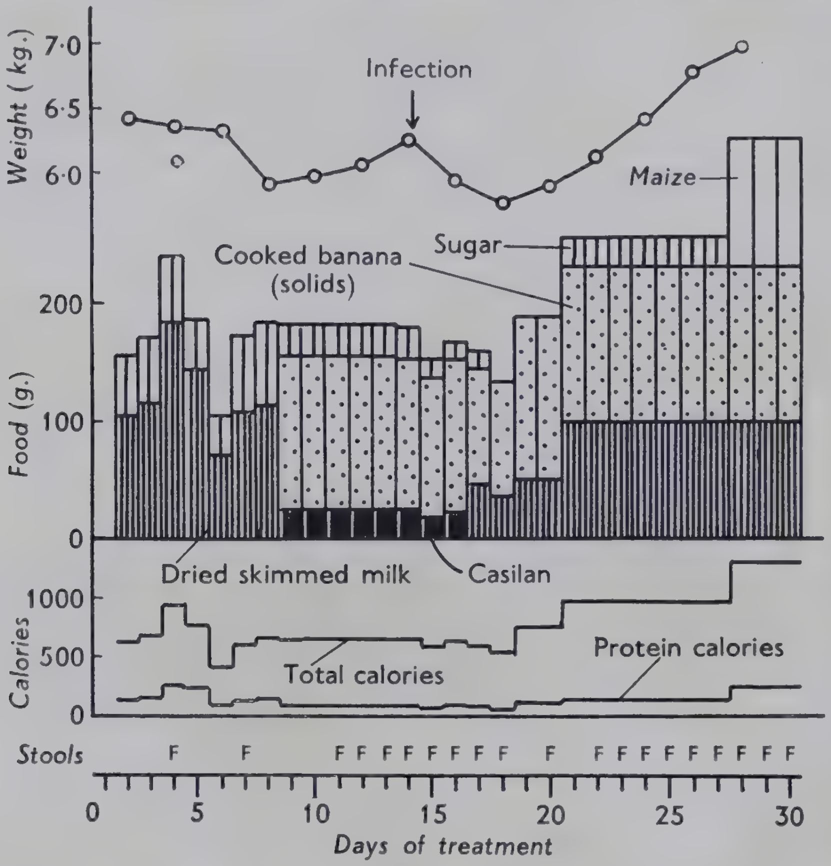


FIG. 22.—Treatment of kwashiorkor with dried milk, Casilan, and cooked banan

The banana probably had a good effect on the stools, and with its aid even maize gruel was finally tolerated well. (Formed stools are indicated by F.) A explained in the text, maize often causes loose stools.

Towards the end of treatment, this child had achieved a satisfactory calori intake, and was gaining weight well. The amount of protein taken daily seldor exceeded 25 g.

stools at once improved, and stayed good until the former quantit of dried skimmed milk was given, with a smaller amount of sugar when they deteriorated promptly. A return to the skimmed milk high protein mixture again improved the stools, and finally, wit the continued betterment of the child's general condition, the remained formed although the amount of skimmed milk was raised in two steps, to 140 g.

Moderate amounts of skimmed milk, fortified with the proprietar lk protein preparation so that the children could be offered o to 150 g. protein daily, have been used extensively at Kam- la. The mortality which could be attributed to uncomplicated vashiorkor was between 5 and 10 per cent, most of the deaths curring shortly after admission or unexpectedly in children who emed to be on the way to recovery (see p. 114). The remarkable eed at which oedema was lost, the skin began to heal, and the cture of misery was changed, agreed with the experience of other orkers. The accompanying biochemical changes are described page 207.

A change of some importance was introduced to circumvent e carbohydrate intolerance. This was the use of banana, either e cooked variety (plantains : *Musa balbisiana*) or the sweet (*Musa pientum*). The observation that a few children when they first me to hospital passed formed stools containing recognizable lumps the cooked banana led to the trial of that food ; it was afterwards perseded by the sweet banana which seemed to be more completely gested, especially if it was mashed and allowed to stand for half day, in which time a bland collection of carbohydrates, mostly uctose and glucose, was produced. These carbohydrates had a easing taste that nearly all children liked, even when they were ry ill, and sweet banana-skimmed milk diets became very popular. ne diets could be made thick or thin by the addition of different nounts of water, so that they could be eaten with a spoon or given rough a stomach tube. For the children who needed a soft diet, gested as easily as possible, it was found best to pass the mixture rough a high-speed blender, which produced a smooth creamy od. It tasted only slightly of the skimmed milk powder, especially 25 to 30 g. of sugar was added.

At first, it was the custom to add cautiously small amounts of maize porridge described above, the addition being used partly a trial of returning enzyme function (p. 215). If the porridge s well tolerated, it was considered safe to proceed further towards nixed diet. After some experience had been gained, however, s policy was changed, and it became customary, throughout the days which represented the duration of the stay in hospital of a erely ill child for a complete course of treatment, to keep to the h protein diet, with the minimum of additions. To some extent, s policy was dictated by circumstances, more perfect control of diets being possible if no additions were allowed.

The introduction of new foods into the diet of a child wh seems to be responding well to treatment must necessarily be empirical matter, determined by the condition of the individual chi and by the foods locally available. At the time of writing one us (H. C. T.) has formed the opinion that good results can obtained by adding cooked banana (plantains), or well-cooked bean or groundnuts to the mixture of dried milk and sweet banana. Th combinations produce rapid weight gains, and are usually mo satisfactory than any combination that includes a maize grue Maize seems more likely to produce loose stools than does th cooked banana.

To summarize, it can be said that experience in Kampala, an the results obtained elsewhere, suggest the following scheme treatment for severe cases :

(*a*) Take 400 g. peeled sweet bananas, mash with a fork, sprea out in a shallow dish and allow to stand for 6–8 hour

(*b*) Take 200 g. dried skimmed milk, stir into a smooth past with a little cold water, add hot water to a final volum of 500 ml. and heat to boiling. Allow to cool.

(*c*) Mix the banana and the reconstituted milk thoroughly, possible in a high-speed electric blender, adding up 70 g. sugar.

(*d*) Divide the mixture into six or eight equal amounts. Fee with a spoon.

A diet made in this way provides about 75 g. protein and 120 calories. The total amount will probably not be taken by the chil in the first day, but that is unimportant : the appetite should b better the next day.

If the child will take nothing from the spoon, the most convenien form of feed is a mixture of 100 g. dried skimmed milk and 50 calcium caseinate (the preparation used most in Kampala has bee Casilan, made by Glaxo), in water to a final volume of 500 ml. Th mixture, which is a little stiff at first, liquefies on standing and passe easily through a gavage tube. Six feeds, each of about 80 ml., ar given in the first 24 hours. It is very seldom necessary in practic to continue tube feeding for more than another day, and the swee banana–dried milk diet (fortified with calcium caseinate if desire can usually be started during the second day, or at latest the thir

Bananas are the best vehicle for the milk protein known to th writers, but they are not indispensable : the sweetened milk feed ll usually be found acceptable by themselves. Substitutes for the nana can undoubtedly be found : semolina, rice, cereal flours, tatoes and even cassava " flour ", are probably worth trying. The ols rapidly indicate intolerance.

Treatment with plant protein diets

On the basis of the conception of kwashiorkor as a protein-ficiency disease, and with the knowledge that in other circum- ances, undernourished children could be fed satisfactorily on all- ant diets, there seemed to be no obvious reason why kwashiorkor ould not yield to treatment with diets containing protein exclusively plant origin. This theory was tested by using mixtures of sweet nana and soya. The rat experiments which were being carried t at Kampala had showed that the combination was valuable, but ey also showed that growth was extraordinarily stimulated by the dition of a vitamin mixture. This mixture, originally intended a blunderbuss vitamin supplement that might be expected to ercome any vitamin deficiency, had the following composition. ne g. provided 0·6 mg. thiamine mononitrate, 0·9 mg. riboflavin, 0 mg. nicotinic acid, 1·0 mg. calcium pantothenate, 0·3 mg. ridoxine hydrochloride, 0·6 mg. folic acid, 2000 U.S.P. units tamin A, 400 U.S.P. units vitamin D, 20 mg. ascorbic acid, and reptomyces fermentation extractives with an activity equivalent to at of 6·0 μg. vitamin B_{12}. The methionine content of the mixture as believed to be negligible.

The sweet banana was used, as before, uncooked and matured standing after it had been mashed. The soya was prepared in e following way. Washed beans were soaked overnight in about e times their volume of water ; they swelled to more than twice eir original size, and their brown skins could then be rubbed off sily and washed away. They were put through an ordinary kitchen ncing machine and were packed into glass jars of the kind used Europe for the domestic bottling of fruit. An empty space ut 5 cm. deep was left at the top of the jars, which were then ost filled with water, and the patent screw caps were fitted on sely. The jars were placed, 10 to 15 together, in a large saucepan taining enough water almost to cover them. The lid was put the saucepan and the jars were heated by boiling for 8 to 10 irs. (An earlier method, in which the boiling was carried on a shorter time and followed by autoclaving, was superseded by this method when animal experiments had shown that it produce satisfactory results.) The soya prepared in this way seemed to kee perfectly in the sealed jars for a month or more. It was quite sof and could be made into a smooth paste by rubbing between th finger and thumb. It had a faint and not unpleasant flavour, an had lost altogether the bitter taste often associated with soya. On hundred g. contained 17·0 g. protein and 8·5 g. fat. It was usuall incorporated with the mashed banana in the high-speed blender the vitamin mixture being added at the same time. A day's foo for a child weighing 6 to 8 kg. might consist of 300 to 400 g. of th mashed banana, 300 g. of the soya preparation, 25 g. sugar (sucrose and 2·0 g. of the vitamin mixture. This diet provided a little mor than 50 g. protein, and about 1000 calories. It also provided nearl 25 g. fat, but apprehensions of the danger of giving so much fat based on some unfortunate experiences with full-cream milk tha had shown only too clearly the fat intolerance of severe kwashiorkor proved to be largely unjustified: the soya fat, possibly becaus its fatty acid composition was very different from that of milk fat seemed to be easily absorbed and did not cause any gastro-intestina upsets, even in moderately severe cases.

Details of the treatment of children with banana-soya diets ar given in Figs. 23 (a) and (b). Little comment is necessary, but i should be pointed out that these children were not amongst thos classified at Kampala as being most desperately ill. For such children it was still, at the time of writing, usual to employ th high-protein milk diets, which were thought to give the greates chance of recovery. For the majority of children not so severel affected, the banana-soya diets seemed to be satisfactory; in a fe cases, however, there seemed to be a definite aversion from soya or the diet would be taken and subsequently vomited. The vomiting was thought to be associated with a tendency to unduly large gastri residues—found sometimes even on the milk diets—and it wa proposed to repeat all the trials of soya, using a de-fatted flou instead of the whole bean. In those cases where a satisfactor intake of protein could be quickly established, the results of usin the plant protein diets appeared to be very little different from thos obtained by using the milk protein diets, but more investigation i needed before an exact comparison can be made. Theoretically advantageous amino acid supplementation could have been achieve by adding a cereal to the banana-soya mixture. In practice, it wa

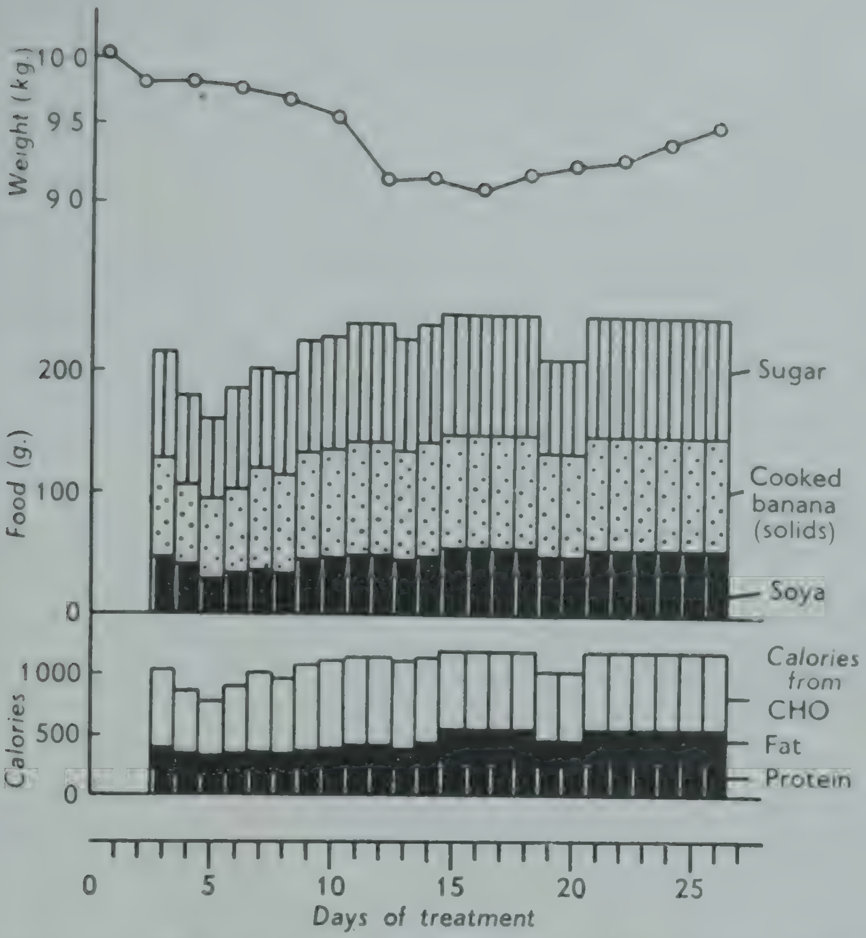


FIG. 23.—Treatment of kwashiorkor with plant protein diets.

(*a*) Use of a soya preparation (described in the text, p. 195) and cooked banana. gress was satisfactory, and the stools were always well formed. The diet tained considerable amounts of soya fat, which provided as many calories as total protein.

Large amounts of sugar were well tolerated.

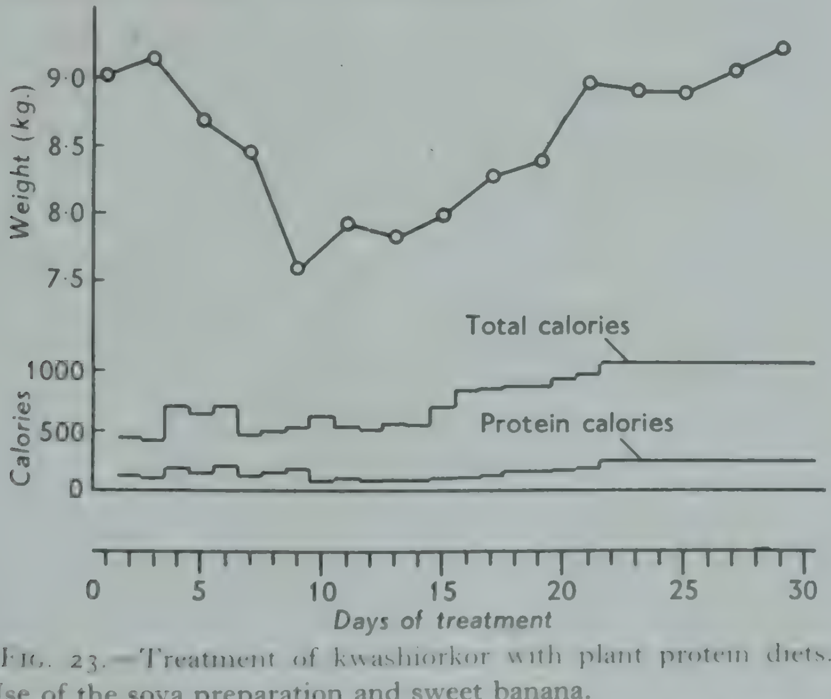


FIG. 23.—Treatment of kwashiorkor with plant protein diets.

b) Use of the soya preparation and sweet banana.

n excellent response, with rapid loss of oedema and regain of weight. At the of writing, such a response is exceptional when plant protein diets are used, the arrest of the disease is usually effected more slowly.

found that the bulk of the cereal, when it had been cooked in suc a way as to make it acceptable, was a serious handicap, and th cereals were not always bland. In the matter of volume and co centration, the plant protein diets were less suitable than the mi diets, but it was clear that they could be greatly improved.

7. Towards a rational treatment

The treatment of kwashiorkor with plant protein diets was development of work which had begun in Germany several yea earlier, when attempts were made to prove the value of diets th contained no animal protein. The attempts were founded on t belief that it might be possible to put together mixtures of amir acids that resembled closely, even if they did not rival exactly, t mixture in milk protein. The German work was carried out wi children who were mildly undernourished, their diets being fair well balanced, but lacking in caloric value. It supported the beli in the value of plant protein mixtures, but it was felt that time, ar wider experience, might bring a shift in emphasis away from detai of amino acid composition: children might be found to be le exacting in their demands for essential amino acids than had at or time appeared likely, and the gap between plant and animal protei might be bridged in other directions. The German work ha recently been reported in full (Dean, 1953).

By the time it became possible to continue the work at Kampal the importance of the 'animal protein factor' had become mo obvious, and it was clear that this factor might be what was neede to raise the value of suitable plant mixtures near to that of the be foods containing animal protein. About the same time, opinio had begun to crystallize into the belief that kwashiorkor was a diseas caused largely by a deficiency in protein. It was also becomin clear that if this belief was upheld, there was little hope for th good health, and even the lives, of a great many children unless som really adequate vegetarian diet could be evolved: the pressure c economic circumstances would make any large-scale relief of th conditions causing kwashiorkor impossible, if prophylaxis wa dependent on the provision and maintenance of a supply of anima protein. Animal protein is expensive, and is likely to remain sc It is expensive in terms of land, labour, materials and time; th most efficient animal returns as edible products only a small propor tion of the nitrogen it is fed (Boyd, 1951) and although a good cas n be made out for a scientific combination of plant and livestock isbandry (Blaxter, 1951) the countries in which kwashiorkor ourishes are mostly those in which the livestock element is reduced absent.

A cheap treatment for kwashiorkor seems to be essential. Milk established as the treatment of choice in the most severe cases, it it is costly. Some attention to the reasons which have made ilk the treatment of choice may be a justifiable digression. It ould at least indicate some of the virtues of a practicable, if not tirely ideal, substitute.

In the first place, milk is a convenient source of protein of high ological value. Dried skimmed milk contains about 34 per cent otein, and 150 g. will provide the 50 g. protein which seems, om Kampala experience, to be needed daily if even a mild case kwashiorkor, in a child aged 2 to 3 years, is to be cured. At rrent prices, 150 g. costs 50 E. African cents in Uganda, the uivalent of sixpence in British currency. It often seems preferle, however, to give 100 g. protein daily. No child was found no could tolerate so much as the 300 g. skimmed milk needed to ovide this amount of protein. The concentrated milk protein pplement which was used cost approximately twelve times as uch as the skimmed milk protein, which made it hopelessly ipracticable for anything except special use.

The 150 g. dried skimmed milk would yield, in addition to the g. protein, about 1·7 g. methionine, 240 mg. choline and 15 μg. amin B_{12} (Table 11). These figures are probably only very ughly accurate, but will serve the present purpose. Which of e three items—methionine, choline or vitamin B_{12}—should be garded as the agent responsible for effecting cures? Were they mplementary to each other, or were one or two of them superous? If one was reduced in amount, would the others have to increased to obtain a good effect? Was some other ingredient, h as an amino acid, indispensable? These are all questions that nnot be answered at the present time, but it can at least be said t the choice of milk, however empirical it may have been in the t instance, has the support of analytical data.

As mentioned above, satisfactory results have been obtained at mpala by the use of diets containing banana, soya and a vitamin ture. The banana had only about 1·5 per cent protein, and hing is known about the amino acid composition of that protein,

TABLE 10

Nitrogen and fat balances of children

Name	Condition	Diet	Nitrogen						Fat	
			Food g.	Urine g.	Faeces g.	$\frac{\text{Urine N}}{\text{Faecal N}}$	Absorption %	Daily balance g.	Food g.	Absorption %
Mawanda	Acute kwashiorkor	Soya and banana	25·6	6·8	7·2	0·9	72	+ 2·9	96·0	86
,,	After 25 days' treatment	,,	12·6	7·7	2·6	3·1	79	+ 0·6	62·5	96
Bandiho	Recovering kwashiorkor	,,	26·6	11·4	6·4	1·8	79	+ 2·2	116·2	94
Kisule	Polio convalescent	,,	28·2	15·7	5·6	2·8	80	+ 1·7	117·0	97
,,	,,	Skimmed milk and banana	23·9	13·6	2·8	4·8	88	+ 1·9	—	—

The length of each balance period was 4 days, and nitrogen absorption was calculated as $\frac{\text{Food N} - \text{Faecal N}}{\text{Food N}} \times 100$.

The important points are (*a*) the increase in nitrogen and fat absorption by the child Mawanda, after 25 days' treatment, (*b*) the similar results obtained by giving the banana diet to Bandiho (see Fig. 25, p. 206), who was recovering from kwashiorkor, and Kisule, who had never had kwashiorkor, and (*c*) the improvement in nitrogen absorption when Kisule was given a milk protein diet.

xcept that it may be lacking in methionine. Fifty g. soya protein, ne amount in 300 g. of the prepared bean paste, contains approximtely 1·6 g. methionine and is accompanied by over 500 mg. choline. This large amount of choline is derived from the soya lecithins; ney are split in the body, at least in normal circumstances, into tty acids and choline.) There is no vitamin B_{12} in soya, but the itamin mixture added to the diet provided the equivalent of 12 μg. itamin B_{12}.

From these calculations it seems that the milk and the soya iets, each containing about 50 g. protein, supplied about the same nounts of methionine and vitamin B_{12}, and that the soya diet had large excess of choline. In theory, therefore, the diets should ave given similar results, and it was so in practice, with the proviso iat the soya was given to those children who were not the most eriously ill, and might therefore have had less impaired digestions. in the future substantial differences are noticed in the efficacy the plant protein and the milk diets, it will presumably be necessary look for an explanation elsewhere than to total protein, methionine, tamin B_{12} or choline. It will of course be necessary to bear in ind that the absorption and utilization of these substances from ie two kinds of diet may be different; the result of a single air of balance studies, made on a child with none of the signs of vashiorkor (Table 10) suggests that there may be differences of me importance.

In theory, there seems to be no reason why a number of other mbinations of foods should not be used for the cure of kwashiorkor, though some ingenuity may be needed to prepare them in a form itable for the children. The amounts of protein, methionine and tamin B_{12} in various foods that might be employed are given in able 11.

If future work shows that vitamin B_{12} is essential, it will be cessary to find a cheap source, as this vitamin, despite a few reports the contrary, is probably not to be found in any plant, or in asts. It may be necessary to use wastes from antibiotic manucture, which ought to be very cheap in a dried form, or even to rt the production of a crude form of the vitamin, using some of e many micro-organisms known to produce it, and omitting any t the most essential steps in purification. The plant diets should herwise be quite inexpensive, provided that locally-grown materials be used. In Kampala the price of soya beans during 1952 was

TABLE 11

Amounts of various foods yielding 50 g. protein and the methionine, choline and vitamin B_{12} they contain. (*From Dean,* 1952 *Proc.* b)

Food	Amount of food g.	Methionine g./50 g. protein	Choline mg./50 g. protein	Vitamin B_1 μg./50 g. protein
Meat (beef muscle) . .	250	1·6	240	15
Fish	250	1·7	210	18
Liver	310	1·6	1650	310
Cow's milk : dried whole .	190	1·7	204	15*
Cow's milk : dried skimmed	150	1·7	240	15*
Maize meal	625	1·5	260	0
White wheat flour . .	500	0·5	260	0
Rice	830	1·7	730	0
Pea nuts (ground nuts) .	180	0·6	300	0
Soya bean	125	0·8	425	0
Soya (Mulago preparation) .	300			

* Maximum figure. Losses in drying may be considerable.

so low that 50 g. soya protein cost only about 10 E. African cent (equal to one British penny); 400 g. sweet banana cost anothe 5 cents, and the cost of the whole diet, excluding preparation an the vitamin mixture, was only a shilling a week for each child.

At the time when treatment with plant proteins was bein attempted in Kampala, a somewhat similar trial was being made a the Children's Hospital in Mexico City. Gomez, Galvan, Bienven and Muñoz (1952) fed a series of groups of malnourished children including some individuals with "third grade malnutrition", or diets containing maize, beans and wheat, to which was added eithe soya or a mixture of milk and yeast. The experiments were carrie on for several months, and the only difference that was noticed i the effects of the two diets was that the total serum proteins rose t the normal level more rapidly when the diet containing milk was bein given. This difference has also been noticed in Kampala. It wa not fully understood, and was thought to need further investigation as it might throw light on mechanisms of protein synthesis.

8. The treatment of infections and complications

The course of a case of kwashiorkor treated with a high-protei diet can usually be predicted with fair accuracy, and a failure t conform to the usual pattern should raise the possibility of a complicating disease.

Although too much attention was probably paid at one time t the infections that often accompany kwashiorkor, and too little t the disease itself, the danger of overlooking an infection must no be underrated. The danger is all the greater because the usual reaction of fever and leucocytosis may be absent, or slight. All bacterial infections should be treated in the usual way with sulphonamides or antibiotics, for which there is no discernible intolerance, and which do not seem to have less than their usual potency. Malaria, with adequate treatment, appears to run its usual brief course, but it is the practice at Kampala to give some prophylactic anti-malarial drug throughout treatment for kwashiorkor. Diarrhoea, at one time considered almost invariably to be due to intestinal flagellates, helminths or bacteria, and still on rare occasions caused by one of these agents, should respond so quickly to correct dietetic treatment that there can be no doubt of the diagnosis.

Antihelminthics and their accompanying purgatives are likely to be lethal if they are used indiscriminately; their use should be postponed as long as possible. It may be considered contrary to the first principles of treatment, and to common sense, to give a iver poison to a liver already damaged, and a purgative to a gut already over-sensitive. If there is severe hookworm anaemia, which s itself a danger to life, the best treatment is probably to give one or more blood transfusions, with extreme care that the transfusion runs slowly, as a supporting measure that will tide the child over until the worms can be removed with less acute danger. In Kampala, ferrous sulphate and other iron salts have usually been found to produce very little alteration in the level of haemoglobin, especially n the early stages of treatment, and sometimes to give rise to an larming diarrhoea, even in a child who seemed to be safely past the critical phase. Autret and Behar (1954) say that Central American doctors advocate that the dosage of iron should be small at first, and ncreased slowly, and that hydrochloric acid should be given at the same time, to facilitate absorption.

Very little is known about the harmful effects of a small load of hookworm, but it is certain that even in severe kwashiorkor, the effects may be of very little importance. In the same way, the inding of an occasional malaria parasite in the blood of a child, as he result of a long and careful search, does not of itself constitute he diagnosis of a malarial condition likely to endanger health or to mpede recovery. Discretion must, in kwashiorkor, be allowed to be the better part of therapeutics.

The infection which most commonly complicates kwashiorkor without being obvious, and which may be the cause of prolonged failure to respond to the full and correct therapy, is tuberculosis If the disease is not too far advanced, it will usually respond wel to streptomycin, but it has been remarked that in children wit kwashiorkor complicated with this infection, the hair regains it usual colour even slower than usual. If any severe condition i superimposed on kwashiorkor, such as leprosy, sickle-cell anaemia, kala-azar, chronic nephritis or neoplastic disease, few, if any, of the signs of kwashiorkor are likely to disappear, however perfect may be the dietetic treatment.

THE RESULTS OF TREATMENT

1. Clinical changes

The successful treatment of kwashiorkor is remarkably satisfactory, in the rapidity with which its effects became obvious. Many writers have commented on the rapidity, particularly in the loss of oedema. It is generally agreed that the healing of the skin proceeds more slowly, although it may begin within a few days, and that the restoration of pigment may take several weeks. This has certainly been the Kampala experience. A few children who have been under observation there for long periods have shown that the time taken for hair to return to the normal black colour and crisp texture may be several months ; alterations in the hair may in fact be one of the first signs to appear and one of the last to disappear. The older pale hair does not change in colour : the new hair grows at the roots of the old, or in the temporal patches which have gone bald in the acute stage of the disease (Fig. 24).

The loss of oedema is often spectacular, and the body weight may be reduced by as much as 30 per cent, as occurred in several cases at Kampala. The average loss in a series of 60 consecutive cases was 16 per cent of the body weight, and although the cases were for various reasons not fully representative, this figure probably expresses the general course of events. The loss was often complete at the end of the fourth or fifth day of treatment. Less dramatic, but equally important, were such signs as return of appetite and the loss of the characteristic hopeless apathy ; when a child smiled, he was out of danger.

The biochemical changes which accompany clinical improvement are described on page 207. These changes, like most of the others, start very soon after treatment has begun, and with few exceptions re almost completed in 7 to 10 days. After that time, alterations re slight. In some varieties of kwashiorkor, there is said to be onsiderable enlargement of the liver (see p. 99), but with good reatment reduction in size, which must represent the summation f many processes, apparently occurs very rapidly.

There are very few available data concerning the weight gains the period following the loss of the oedema. Hughes (1945–46)

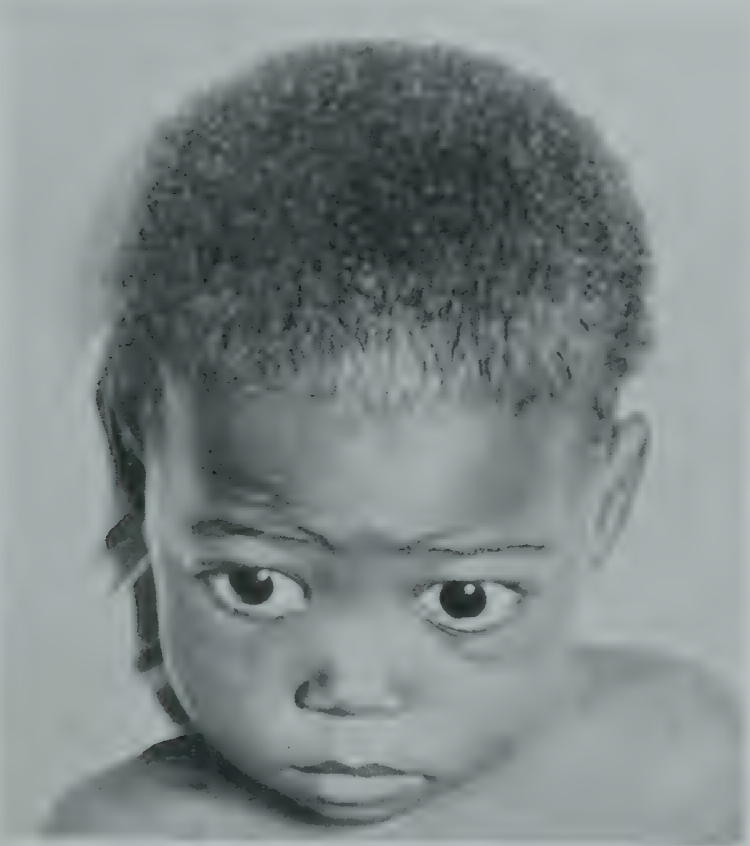


FIG. 24.—Growth of hair during treatment of kwashiorkor.

The new dark hair has filled the temporal regions and is growing low on the head. On the top and sides of the head, the new hair is carrying aloft the which has not recovered its colour or texture.

d that once the children had passed the critical point, weight was ned rapidly. At Kampala the weight chart is not usually conered to be of prime importance in the assessment of improvement ; clinical appearance, the appetite and the reaction to a fuller diet thought to be of more value. It is not unusual for a child to e hospital, at the end of a month's treatment, weighing no more n he weighed on admission, although he is looking very well and ng all he is given. It was at one time thought that there might an impairment of the ability to grow (Dean, 1952a), but it is possible that this view was unduly pessimistic. One child at least, in her reaction to a full diet given for many months, showed that with adequate treatment the stunted child typical of kwashiorkor is not necessarily doomed to remain undersized. The child's record

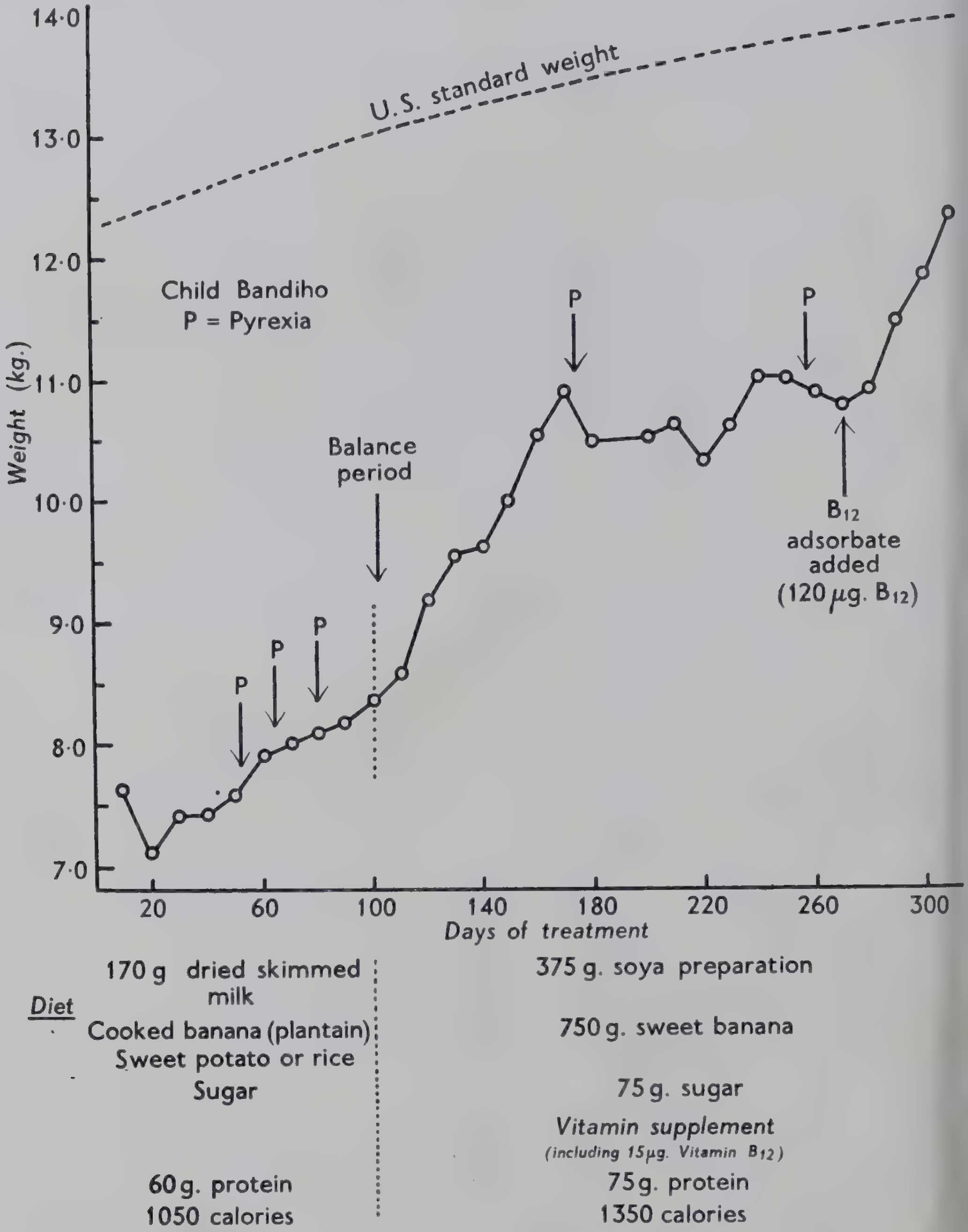


FIG. 25.—Prolonged treatment of kwashiorkor.

The progress of this child, over the whole period of treatment, shows a satisfactory increase in weight towards the U.S. standard. A period of failure to gain weight, from the 170th to the 270th days, was ended when a large supplement of vitamin B_{12} was added to the diet, but this may have been merely coincidence.

For details of the results achieved in the balance period (about the 100th day), see Table 10.

s shown in Fig. 25. She was 5 kg. under the American standard or weight at the beginning of treatment, but grew three and a half imes more rapidly than the normal American child of the same ge, during the year of treatment. The acceleration of her weight ain resembled that of slightly undernourished German children een after the war of 1939–45 (Dean, 1953), and it seemed as though he gain would only be retarded by the physiological limit of growth or a child of her race. The effect of nutrition on what it usually egarded as the physiological limit of growth is an interesting subject or debate.

. Biochemical changes

(*a*) *Changes in the blood.* Certain changes occur in the blood nd other tissues of a child with kwashiorkor when treatment is nstituted. To some extent, these changes depend on the diet, and is unfortunate that most authors have been unable to specify xactly the diets they have used. At Kampala, it has been possible o ensure that the children were given certain diets and to follow he alterations in the blood and the duodenal juice. The account f the changes given here is largely taken, like much else in this hapter, from an account published some time ago (Dean and chwartz, 1953). The children concerned were believed to have o important concomitant disease, and to owe their condition almost ntirely to kwashiorkor. There was no enlargement of the liver or pleen, no pyrexia, no malaria parasites to be found in blood smears, ne Mantoux reaction was negative, X-ray examination of the chest howed no sign of tuberculosis or other infective illness, the urine ontained neither red cells nor casts, the stools contained no cellular xudate or other evidence of an inflammatory condition and, at the ost, only a very few hookworm ova, there was no evidence of ephritis, and the Kahn reaction on the blood of the mother was egative. None of the children was being breast fed ; treatment uring the period covered by the biochemical investigation was ith a diet consisting largely of dried skimmed milk and the comercial calcium caseinate preparation, to which sugar was added improve the flavour and to raise the caloric value. The only her foods which were given were either the cooked banana (*Musa lbisiana*) or the sweet banana (*Musa sapientum*), both of which re added to reduce the tendency to intestinal upset. The amount protein which the diets contained varied from child to child, and during the treatment of the individual child, between 40 and 100 g. daily. The diet never contained more than 2·0 g. fat, at the most.

The children were bled at approximately weekly intervals, and the values found in successive four-day periods were averaged.

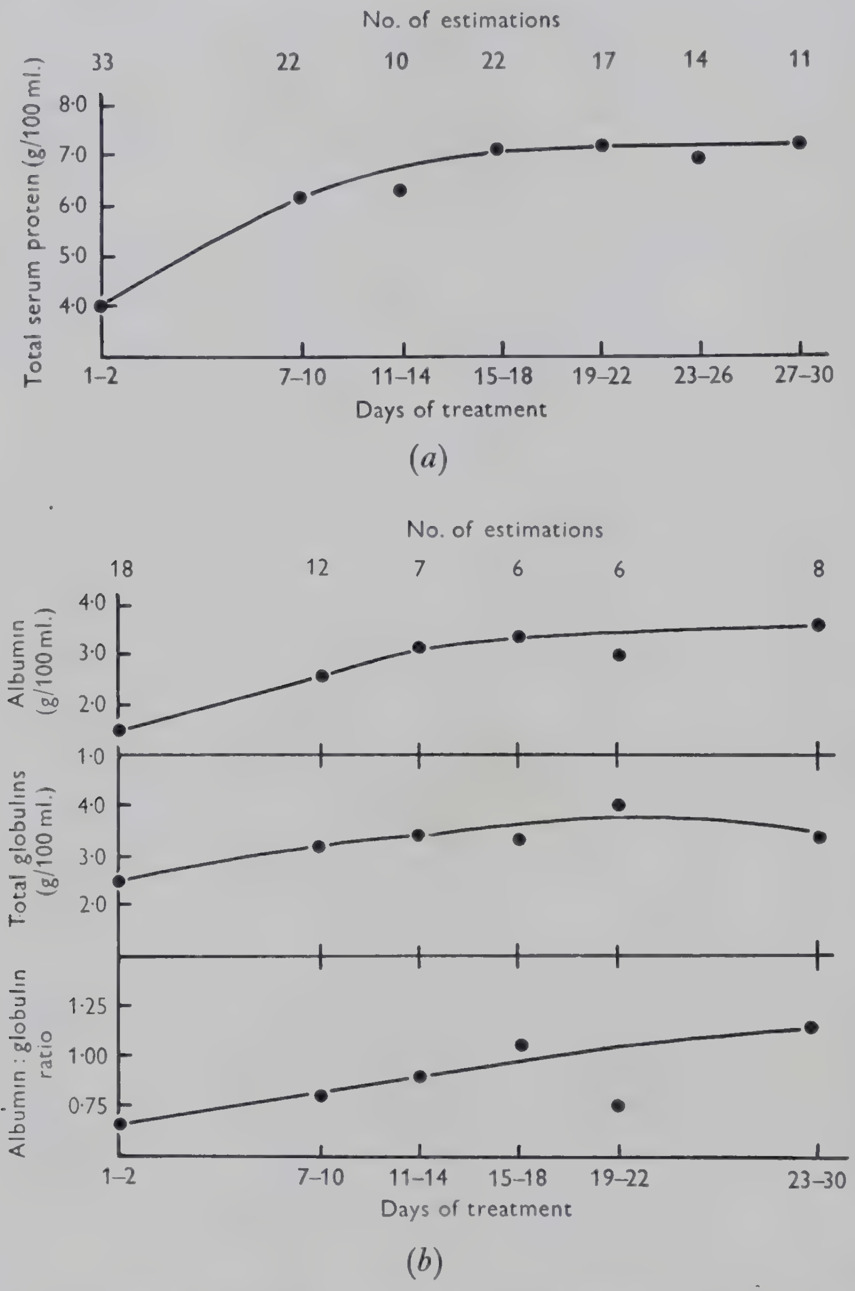


FIG. 26.—Alterations in total protein, albumen, total globulins, and albumen : globulin ratio, urea, total cholesterol and ratio of free to total cholesterol, alkaline phosphatase, pseudo-cholinesterase, amylase and esterase in serum of children treated at Mulago Hospital, Kampala, for kwashiorkor.

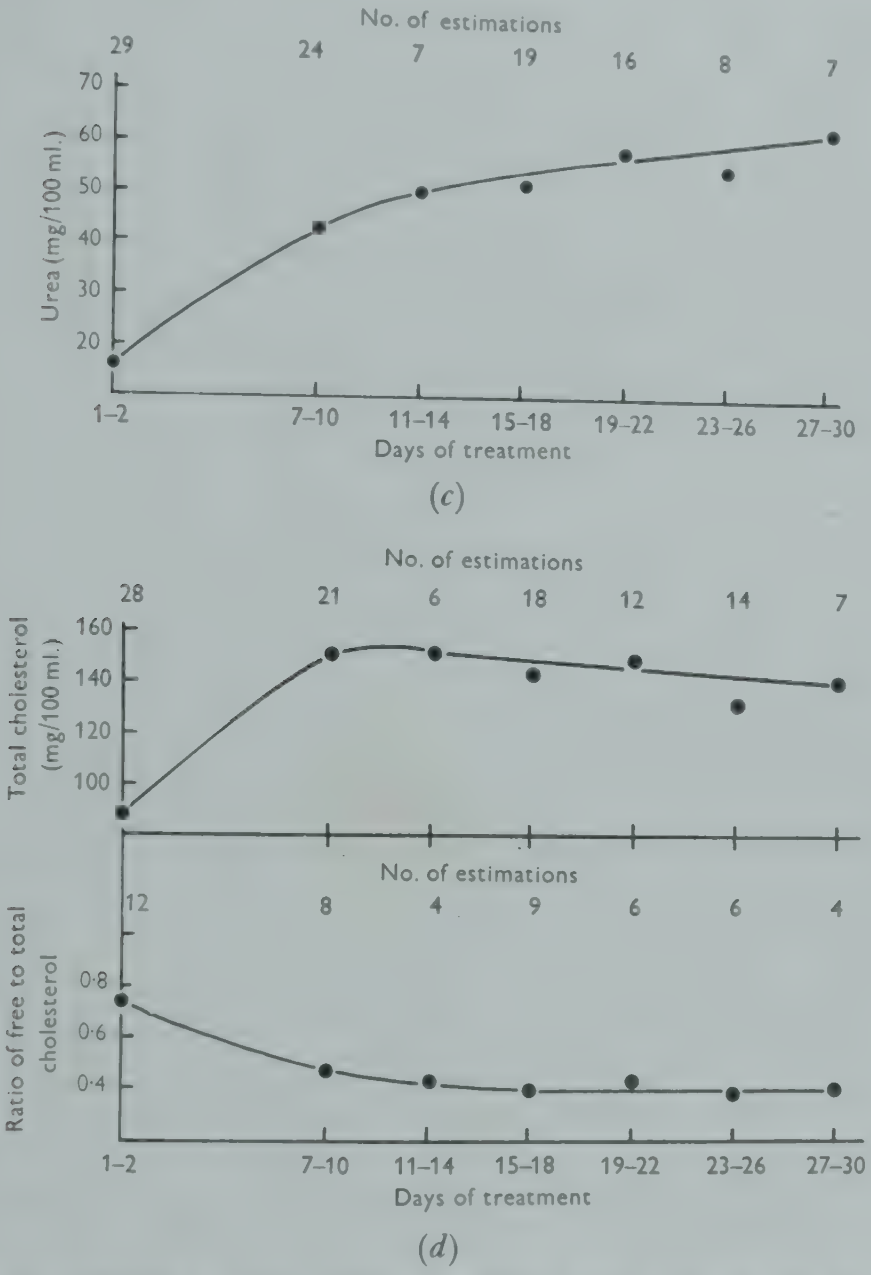
(From Dean and Schwartz, 1953.)

(*a*) Total serum protein.
(*b*) Serum albumen, total globulins, and albumen : globulin ratio.

The results are shown in Figs. 26 (*a*) to (*h*) and can be summarized as follows:

Total protein.—By the 8th day a rise to about 6·0 g./100 ml. had occurred, and the final figure of 7·2 g./100 ml. was reached about the 21st day.

Albumen.—The rise from the 1st to the 8th day—a little more than



G. 26.—Alterations in total protein, albumen, total globulins, and albumen: globulin ratio, urea, total cholesterol and ratio of free to total cholesterol, alkaline phosphatase, pseudo-cholinesterase, amylase and esterase in serum of children treated at Mulago Hospital, Kampala, for kwashiorkor.

(From Dean and Schwartz, 1953.)

(*c*) Blood urea.
(*d*) Total serum cholesterol and ratio of free to total cholesterol.

1·0 g./100 ml.—accounted for slightly more than half the rise in tot proteins in that period. The final average figure was 3·6 g./100 ml.

Total globulins.—The initial level of 2·44 g./100 ml. is close to th usually considered normal for healthy American and British childre The subsequent rise to about 3·6 g./100 ml. was unexpected. Much the rise took place in the first week of treatment.

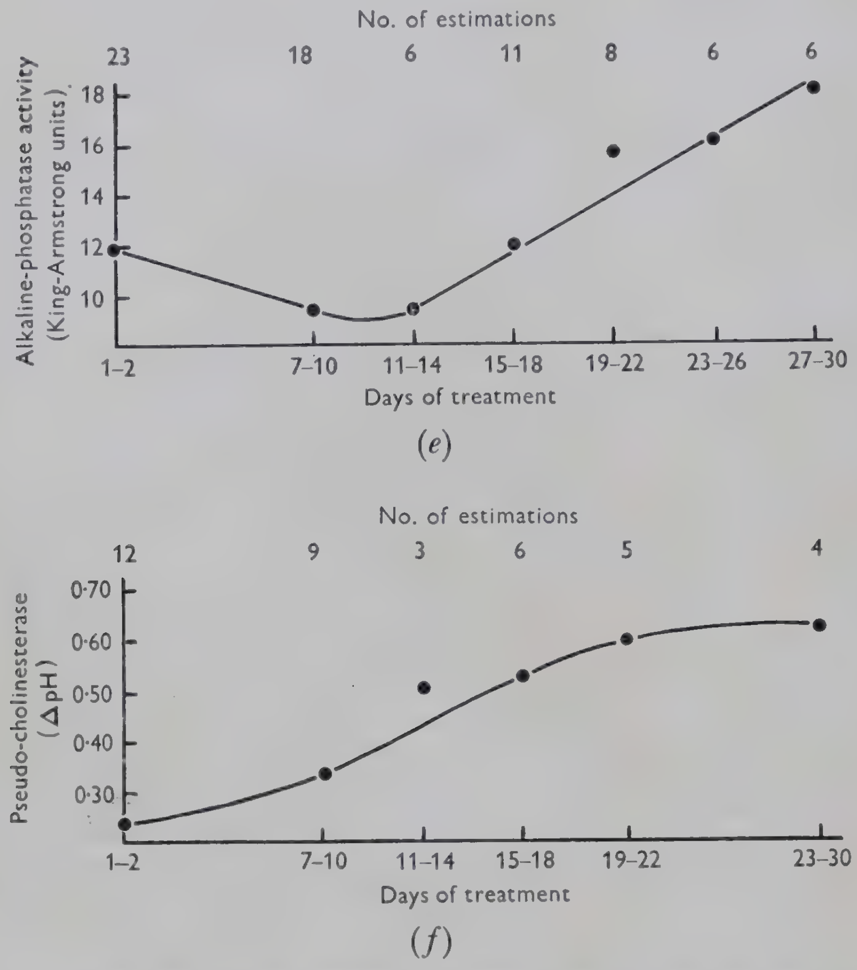


FIG. 26.—Alterations in total protein, albumen, total globulins, and albumen globulin ratio, urea, total cholesterol and ratio of free to total cholesterol alkaline phosphatase, pseudo-cholinesterase, amylase and esterase in seru of children treated at Mulago Hospital, Kampala, for kwashiorkor.

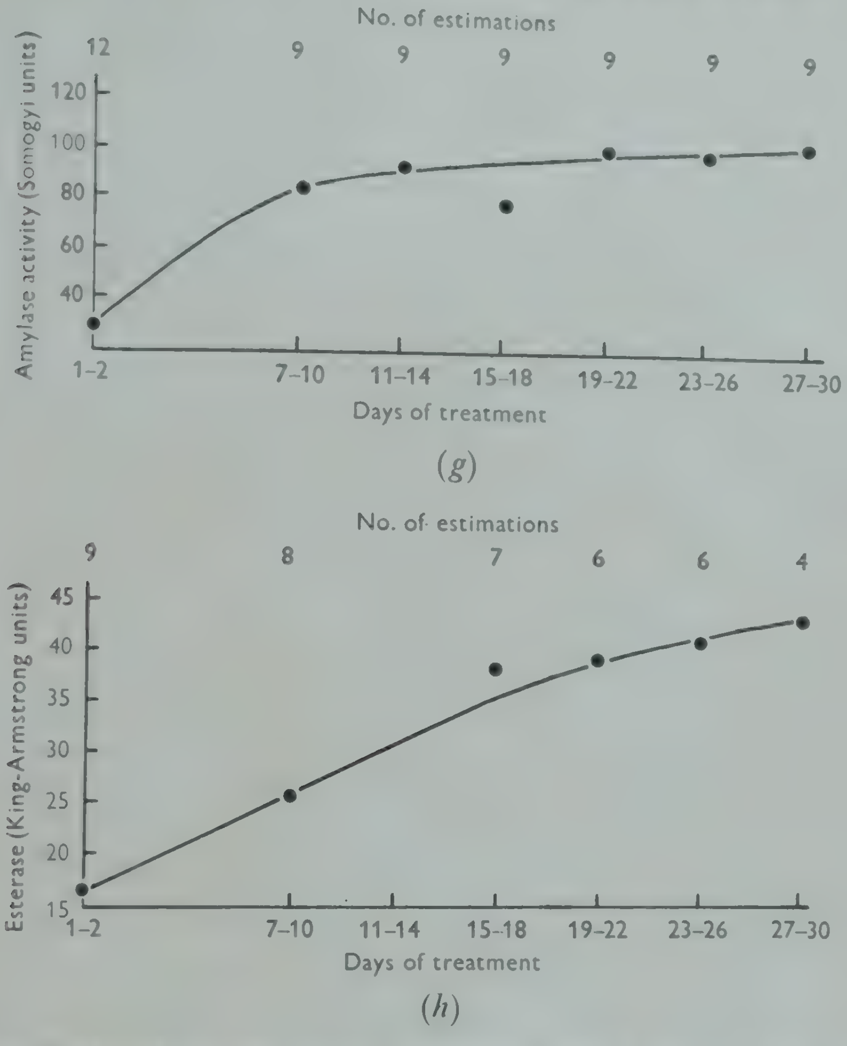
(From Dean and Schwartz, 1953.)

(*e*) Alkaline-phosphatase activity of serum.
(*f*) Pseudo-cholinesterase activity of serum.

Urea.—The peak value was reached about the 21st day. Th average was about 60 mg./100 ml., but one child reached a maximum 90 mg./100 ml. These high values were not accompanied by any sign of uraemia or dehydration, or, as far as could be estimated, by any reduc tion in the urine volume. Towards the end of treatment, the value tended to fall in several cases, although the amount of protein in the die was not reduced.

Cholesterol.—A rise to nearly twice the initial level of total cholesterol ccurred in the first 8 days, but there was afterwards a slight fall, and the nal level was about 140 mg./100 ml.

The ratio of free to total cholesterol showed a rapid fall from the high itial value of 0·76, to about 0·48 on the 8th day, and to 0·40 on the 14th



26.—Alterations in total protein, albumen, total globulins, and albumen : globulin ratio, urea, total cholesterol and ratio of free to total cholesterol, alkaline phosphatase, pseudo-cholinesterase, amylase and esterase in serum of children treated at Mulago Hospital, Kampala, for kwashiorkor.

(From Dean and Schwartz, 1953.)

(*g*) Amylase activity of serum.
(*h*) Esterase activity of serum.

. It was noticed that the ratios, and their change, were very much the ne in all the children.

Alkaline phosphatase.—In 10 of 20 children there were falls in the level his enzyme between the 1st and the 8th days. The average for all the ldren on the 8th day was 9·5 King-Armstrong units. Subsequently re was a fairly steady rise, so that by the 8th day the average was 18 units.

Cholinesterase.—There was a steady rise in the activity of this enzyme, the average at the end of 28 days being about two and a half times greate than the initial value.

Amylase.—The values rose rapidly in the first 8 days, and then attaine a level of about 90 units. By the 28th day the average was about 100 units but there seemed to be a wide range—between 50 and 150 units.

Esterase.—There was a steep rise in the values for this enzyme unti the 15th day, when the average was 43 units. The estimation produce very consistent results.

These Kampala results agree with what has been found else- where during the successful treatment of kwashiorkor. Othe authors (for example Janssen and le Roux, 1950a) have commente on the rapidity with which the total serum proteins increase Anderson and Altmann (1951) recognized that the total globulin might increase, and that the greatest change probably occurred i the γ-globulin, because the thymol turbidity test and the flocculatio test (both of which depend, in all probability, on γ-globulin) ofte become positive. The recovery of enzyme activity follows the sam trend as that found by Waterlow in his investigation of seru cholinesterase (1950), and by Srinivasan and Patwardhan (1952) who estimated serum esterase and lipase separately.

Anderson and Altmann (1951), some of whose results hav already been quoted, analysed by electrophoresis the sera of childre who had been under treatment. Eight of these sera had tota proteins between 6·9 and 7·8 g./100 ml., and may perhaps therefor be considered to resemble the sera of Kampala children at the en of a period of high protein treatment. The results of the fractiona- tion of the sera are shown in Table 12. The total serum proteins

TABLE 12

Components of sera from treated cases of kwashiorkor (called " malignant malnutrition ") analysed by free electrophoresis

(*Data selected from Anderson and Altmann,* 1951)

Case No.	Total protein g./100 ml.	Albumen %	Globulin α %	Globulin β %	Globulin γ %	A/G ratio
2	7·5	53·3	14·6	11·5	20·5	1·14
4	6·9	50·8	9·7	14·4	25·3	1·03
5	7·3	45·1	10·1	16·8	28·2	0·82
6	7·3	51·3	14·0	14·3	20·3	1·06
10	7·1	43·1	11·6	15·5	29·8	0·76
11	7·8	47·4	10·5	13·9	28·2	0·90
12	7·6	45·9	13·9	16·0	23·9	0·85
13	7·3	59·0	5·9	11·4	23·7	1·44
Average	7·3	49·5	11·3	14·2	25·0	0·98

As explained in the text, only cases in which the total serum proteins were between 6·9 and 7·8 g./100 ml. have been included in the table. The sera were from children who had apparently been successfully treated.

raged 7·3 g. 100 ml., and there was approximately 49 per cent umen, 11 per cent α-globulin, 14 per cent β-globulin, and 25 per t γ-globulin. These results are nearly the same as those obtained m 10 Kampala children who had been successfully treated ıble 13).

TABLE 13

*nponents of sera from treated cases of kwashiorkor * analysed by electrophoresis (paper separation)*

(*Data from Thompson,* 1953, *personal communication*)

			Globulin			
ne	Total g./100 ml.	Albumen %	α %	β %	γ %	A/G ratio
	6·20	44·2	15·3	12·8	27·5	0·79
	6·56	45·0	13·6	10·4	31·0	0·82
ou	6·20	47·1	13·8	13·6	25·5	0·89
	6·20	38·5	13·8	9·1	38·4	0·62
	6·93	43·8	18·5	11·5	26·0	0·78
	6·93	53·5	13·2	10·7	22·5	1·14
n	7·60	60·2	10·7	12·0	17·1	1·52
	7·60	37·6	13·0	12·3	37·3	0·60
nu	6·93	52·1	11·9	10·7	25·2	1·09
a	7·60	50·0	11·2	10·8	27·9	1·00
an †	6·87	47·2	13·5	11·4	27·8	0·92
.	*0·55*	*5·8*	*2·1*	*1·2*	*6·0*	*0·22*
mal ‡	7·30	52·6	11·9	8·9	26·5	1·17

* The children are the same as those referred to in Table 4 (p. 167).

† The mean amounts of the protein fractions in 100 ml. serum were 3·26 g. umen, 0·92 g. α-globulin, 0·77 g. β-globulin and 1·90 g. γ-globulin.

‡ Mean results obtained from seven children with unaltered hair and with discoverable infection.

Anderson and Altmann's cases the average amount of albumen from 1·52 to 3·65 g. 100 ml., and in the Kampala series it rose n 1·52 to 3·26 g. 100 ml. In Anderson and Altmann's cases, ever, the average amount of the total globulins rose from 2·48 ·70 g. 100 ml.; in the Kampala series it rose only from 2·78 ·61 g. 100 ml. In Anderson and Altmann's cases the amount -globulin rose by 40 per cent, the amount of β-globulin by per cent and the amount of γ-globulin by 53 per cent; in the npala series the respective increases were 30, 108 and 11 per . No reason can at present be suggested which will account he differences, but it should be remembered that the methods lectrophoretic separation were not the same in the two series. same method of estimation of total proteins (the specific ity method) was used for both series.

he results of estimation by conventional chemical methods, of

TABLE 14

Total protein, albumen and globulin in treated cases of kwashiorkor

All values are for g. protein/100 ml. serum

Author	Number of estimations	Total protein (mean and range)	Albumen (mean and range)	Globulin (mean and range)	Albumen/globulin ratio	Rise from level at beginning of treatment		
						Total protein	Albumen	Globulin
Altmann (1948)	10	7·0 (6·0–8·0)	4·3 (3·6–4·7)	2·9 (2·3–3·3)	1·48	2·8	2·2	0·9
Dean and Schwartz (1953)	18	7·2	3·6	3·6	1·00	3·2	2·1	1·2
Janssen and le Roux (1950a)								
Series (*a*)	8	6·57	3·81	2·76	1·38	2·5	1·8	0·7
Series (*b*)	16	6·28	3·78	2·50	1·51	2·1	1·7	0·4
Van Der Sar (1951)	26	6·66 (5·00–7·50)	—	—	—	—	—	—
	16	—	4·53 (3·66–5·52)	2·13 (1·14–3·00)	2·13	2·5	2·3	0·1

The above results were obtained by chemical methods. For results obtained by electrophoresis, see Tables 3, 4 and 12, 13.

um proteins in the acute stage of the disease and after treatment set out in Table 14.

(*b*) *Changes in digestive enzymes.* The amylase (see Fig. 26 (*g*)) ich was estimated in the sera was probably mostly of pancreatic gin. The results are in agreement with those obtained by ompson and Trowell (1952) who estimated the activity of the ymes in the pancreatic juice after a period of treatment, in which ly large quantities of milk were given. Their results are summarized in Table 15.

TABLE 15

ect of treatment on mean values for maximum concentrations of amylase, lipase and trypsin in duodenal juice of children admitted to Mulago Hospital

(*From Thompson and Trowell*, 1952)

	Number of children	Amylase units	Lipase units	Trypsin units
ated cases of kwashiorkor				
On admission:				
First series . . .	40	0·40	1·00	—
Second series . .	3	0·23	0·40	4·1
On discharge:				
First series . . .	40	4·33	3·88	—
Second series . .	3	2·73	4·13	53·0
al cases of kwashiorkor .	8	0·53	0·81	—
trols	24	2·92	3·84	—

Methods and units are explained by the authors.

The control children had normal hair and no oedema.

In three other children with kwashiorkor values of 2·3, 1·4 and 9·1 units psin were found on admission, and one control child had 56·0 units trypsin.

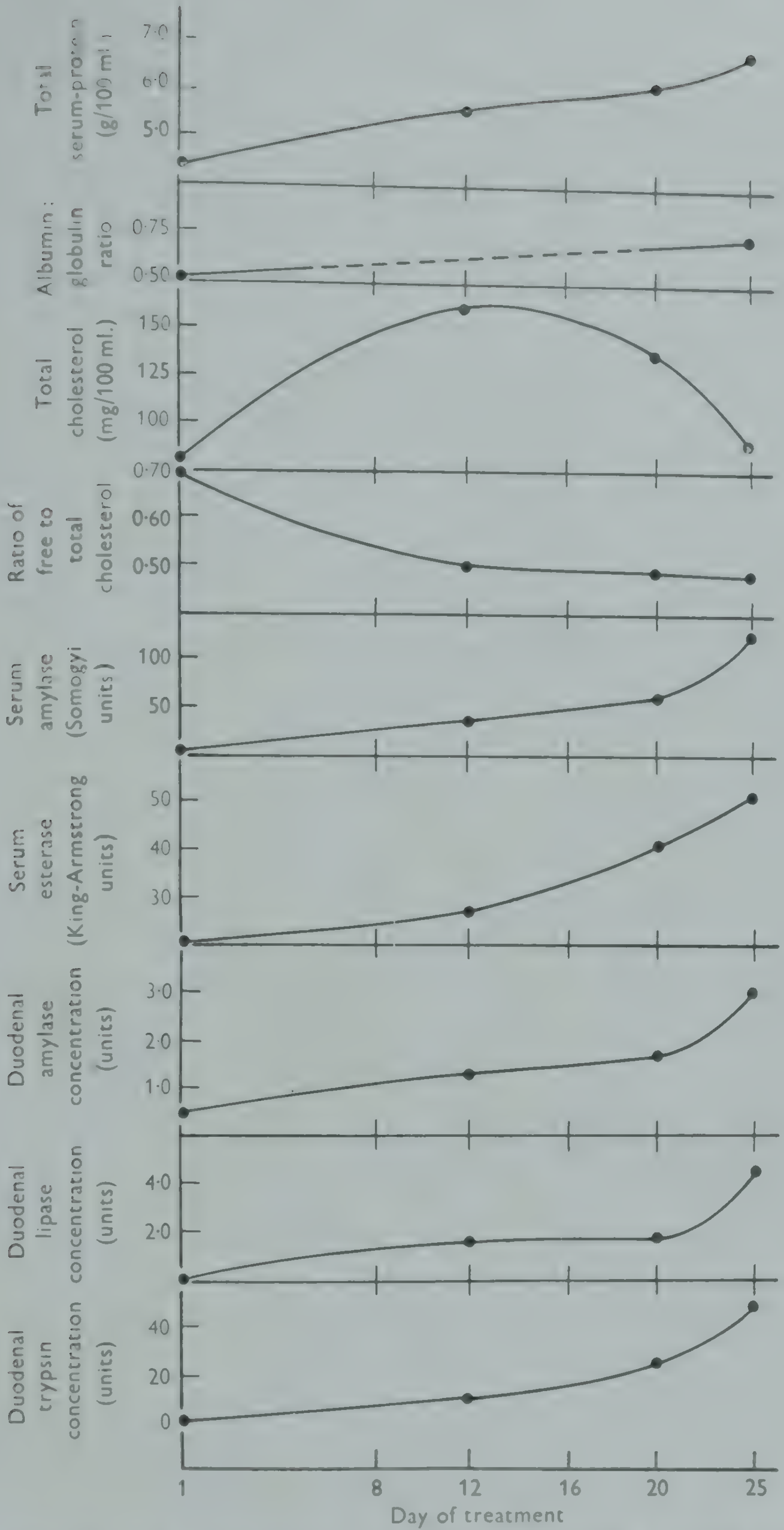
The rises which occurred were clear and unequivocal, and it is haps almost equally significant that in cases where it was impose to establish a satisfactory level of protein intake, a state of irs sometimes brought about by a lack of co-operation on the t of the parents, and sometimes by the aversion of the child n milk, the enzyme levels remained low.

It is reasonable to expect that the recovery in enzyme activity uld increase the digestion of foods, but the proof can only be blished in a quantitative way by the performance of balance lies which are, in children with kwashiorkor, exceptionally cult. The technique evolved at Kampala is imperfect and has permitted the studies to be carried on for more than 4 days, on the whole the data obtained (Table 10, p. 200) confirm the lts obtained by duodenal intubation. A child in the acute stage e disease, but not judged desperately ill, was given a diet of soya and banana which contained about 40 g. protein daily, entirely of vegetable origin, and 24 g. fat. The percentage of nitrogen absorbed was 72, and that of fat 86. The nitrogen in the faeces exceeded that of the urine, indicating that much protein was escaping breakdown The balance study was repeated after the child had been treated for 25 days, always with the same diet of soya and banana, which was accompanied by a mixture of vitamins that included vitamin B_{12} There was a most unfortunate period of anorexia during this second period, and the intake of protein fell to just under 20 g. daily—a circumstance that made the interpretation of the results uncertain It was found that the absorption of the nitrogen had increased 79 per cent and that of the fat 96 per cent. The amount of nitrogen in the urine greatly exceeded that in the faeces, which was believed to imply the increased breakdown and absorption of protein. It was hoped to repeat and extend these balance studies, which, within their obvious limitations, provide a good measure of functional recovery.

Altmann (1950) noticed that clinical recovery might not bring with it normal tryptic activity in the stools. Before treatment trypsin had been found in the stools of only 6 of 41 children (15 per cent) ; at the end of treatment it was present in only 9 of 19 (47 per cent), but the significance of this low proportion is uncertain The tryptic activity should be measured again when nitrogen balances are being done.

The simultaneous alterations in blood and duodenal contents in one child during treatment are shown in Fig. 27.

(*c*) *The significance of the alterations found during treatment.* The simplest explanation of the changes found in the blood after successful treatment would be that the withdrawal of water had caused some degree of haemo-concentration, and Niemeyer, Lopez and Meneghello (1949) think that the apparent recovery of the level of the serum proteins can largely be accounted for in this way. From the amount of weight lost, however, it seemed unlikely that in the Kampala series the plasma volume could have decreased by more than 1/8 to 1/9 when the oedema fluid was removed. The changes in concentration observed nearly always involved more than this fraction, and were not the same for all the substances estimated ; the evidence is suggestive of active regeneration of the substances, as well as a certain degree of concentration. Gomez, Galvan, Muñoz and Bienvenu (1950) estimated the blood volume in cases o



IG. 27.—Simultaneous investigation of serum and duodenal contents in a child treated for kwashiorkor.

The amount of protein in the diet was moderately high (35 g. daily) until the entieth day, when it was increased (to 60 g. daily).

(From Dean and Schwartz, 1953.)

"third degree malnutrition". They found it was consistently higher, in proportion to the body weight, than in healthy children, and that it rose with the percentage of underweight. In children whose weight was 25 per cent less than the expected weight for age, the blood volume was about 130 ml./kg. body weight, but if the weight was 60 per cent less than the expected weight, the volume was about 145 ml./kg. In healthy and well-grown children of the same age, the volume was 100 ml./kg.

There seems to be little doubt that the low level of serum albumen found in the children in the acute stage of kwashiorkor plays a considerable part in the production of the oedema, and that the rise in the level contributes to the loss of the oedema. Many factors are probably responsible for the loss; it has in recent years been recognized that the coming and going of oedema is not a simple matter (Kerpel-Fronius and Varga, 1953).

It is well known that in hunger oedema, there is a considerable increase in extracellular fluid. An increase has also been found in kwashiorkor, or at least in its Italian counterpart, *distrofia da carboitrati*. Passaro (1953a) found values up to 41·5 per cent of the body weight in 9 oedematous children aged from 11 to 24 months who had been fed for periods ranging from 1 to 5 months on high-carbohydrate diets, consisting almost exclusively of cereal foods. There was a considerable fall of the percentage during treatment, to an average of about 28 in five children investigated repeatedly. Passaro (1953b) also made a highly interesting study of electrolytic balance in 5 of the same children. Near the beginning of treatment, average values for plasma (in mEq./l.) were: sodium 124·1, potassium 3·7, calcium 4·4, chloride 91·8, inorganic phosphate 1·8, protein 10·7; total base 135·3. At the later investigations after treatment for from 3 to 5 weeks, the values were: sodium 136·3, potassium 4·5, calcium 4·9, chloride 101·5, inorganic phosphate 2·8, protein 16·6; total base 148·8. As the values were undoubtedly affected by the loss of oedema, it is of interest to calculate the percentage change of each constituent. Sodium, calcium, chloride and total base increased by about 10 per cent; potassium increased by 18 per cent, inorganic phosphate and protein by over 50 per cent. The differences in the percentages, although not easy to explain in detail, at least confirm that during treatment various processes go on at different rates. Frontali (1953) found that by giving potassium salts he could remove slight abnormalities of the electrocardiogram hat he attributed to potassium deficiency. The salts might be made o serve a double purpose: they are known to improve the utilization of amino acids given intravenously (Frost and Smith, 1953).

Venkatachalam, Srikantia and Gopalan (1952), writing from Coonoor, said that in the syndrome they called 'nutritional oedema n children' the extracellular fluid of the body was greatly increased n amount, but the amount of intracellular water was normal: both mounts fell during treatment. There did not appear to be any bnormal sodium retention in the acute stage of the disease; the erum sodium and potassium were at the normal levels, but the hloride was usually lower than normal, findings that were remin- scent of those in Addison's disease. It was considered that in view f these findings, there was no virtue in restricting the amount of salt n the therapeutic diets—a point that was discussed again by the same uthors in a later paper on the electrolytic changes in hunger oedema n adults (Srikantia, Venkatachalam and Gopalan, 1952). The roduction of oedema in the children was explained as a process hich began with damage to the liver. The hormonal control of ater balance was upset by the inability of the liver to destroy anti- iuretic substances: the excess amount of those substances circulat- ng in the blood produced an oliguria, and the blood became diluted y the water which the kidneys could not remove. The haemo- ilution caused capillary damage, and fluid escaped into the inter- titial compartments.

It is possible that a sequence of events of a similar kind may equently occur in kwashiorkor. One of the chief objections seems o be the necessity to postulate continued production of anti- iuretic hormone, or even over-production, as well as failure of he mechanism for destruction. Even that is not impossible; it likely that acute kwashiorkor does not affect the activity of all nzyme systems (p. 223), and in the same way, it may not affect he production of all hormones.

It was not quite clear from the paper of Venkatachalam *et al.* o what extent they had found experimental proof for their theory, though Gopalan (1950) had reported an apparent increase in the mount of anti-diuretic substance in the urine of men suffering from dvanced nutritional (hunger) oedema. In some work recently rried out at Kampala, Heller (1953, personal communication) und abnormally high concentrations of anti-diuretic substances the blood in some cases of acute kwashiorkor, and smaller concentrations after successful dietary treatment of those cases. Th reason for the high concentrations could not be exactly established it is Heller's view that the part played by the liver in the destructio of the anti-diuretic substances is not yet known with certaint Various kinds of liver damage are associated with reduction i urinary output (Shay, Kolm and Fels, 1945), but organs other tha the liver may be involved in the removal of anti-diuretic substance from the blood (Ginsburg and Heller, 1953).

An abnormality of the suprarenal cortex, which is believed t control the retention of sodium and water, might conceivably occu in kwashiorkor ; the possible mechanisms have been discussed b Miranda (1948), who suggests that the functions of the gland may b affected in various ways by what he calls " hypoproteinosis " Cortical and medullary functions may be affected to differin extents ; in some of the undernourished children investigated b Gomez, Frenk and Galvan (1951), the injection of adrenocorticotrophic hormone produced a normal response in the eosinophi count, but there was a poor response, particularly if the initial coun was high, to the injection of adrenaline. The repetition of the wor in established cases of kwashiorkor might lead to some interestin findings which could be linked to other evidence of altered suprarena metabolism (see p. 273). It would not be very surprising if som alteration in tissue permeability was also to be found, although ther have been contradictory reports on the state of the capillaries in the oedema of undernutrition (McCance, 1951) ; if there is increased permeability it may be caused by a lack of choline, and reduced by the addition of choline to the diet (Bloem and Neumann, 1953). Tissue tension (also discussed by McCance) may be of importance in the production of oedema, and it may be that the elastic fibres in the skin and subcutaneous tissues, which help to maintain the tension, are altered in some way. It is obvious that much work remains to be done before the oedema of kwashiorkor is fully understood ; it is also obvious, however, that one of the principal factors may be that which is most striking—the very low level of the serum albumen.

There are some important differences between undernutrition of the kind associated with insufficiency of calories in the diet, and kwashiorkor, and the differences are discussed elsewhere (p. 117); there may also be important differences in the causation of the oedema that accompanies the two conditions. Widdowson (1951) reported that in response to a high-protein diet given in quantities limited only by appetite, there was a rise in the average total protein of 19 adults admitted to hospital for the treatment of their hunger oedema, and that the rise was brought about entirely by a rise in the serum *globulin*. The connection between this rise, and the rise in globulin during the treatment of kwashiorkor, is an interesting subject for present speculation and (it is to be hoped) for future investigation. Widdowson did not investigate the globulin fractions in her subjects, but Keys, Brožek, Henschel, Mickelsen and Taylor (1950) found no remarkable alteration in men in whom hunger oedema was produced experimentally ; Gsell (1945), however, found in two subjects who had acquired hunger oedema in German concentration camps, albumen globulin ratios of 1·18 and 0·97, with 9·8 and 7·9 per cent α-globulin, 11·9 and 17·9 per cent β-globulin and 24·1 and 25·0 γ-globulin. The contradiction might be accounted for by differences in the severity of the general condition : it is possible that when undernutrition is very extreme, it is accompanied by large changes in the serum proteins. The changes may include a discrepancy between the colloid osmotic pressure of the serum found by direct measurement and that to be expected from calculations based on the quantities of the isolated proteins—a discrepancy reported by Govaerts and Gregoire (1941), but not confirmed either by Widdowson (McCance and Widdowson, 1951) or by Keys *et al.* (1950).

The ratio of albumen to total globulins in the sera investigated by Govaerts and Gregoire was much lower than that found by the other workers. In sera showing such great abnormality, it might be worth while to attempt a quantitative measurement of the amounts of the amino acids in each of the protein fractions.

The rise in the total globulins during the treatment of kwashiorkor, and the distribution of the rise amongst the α-, β- and γ-fractions, is an interesting phenomenon for which there seems to be no obvious explanation. It is generally supposed that the γ-globulins carry the immune bodies ; it seems to be the general opinion that children with kwashiorkor are at least as susceptible to infections as normal children, and it is unlikely that the high level of γ-globulin in their serum confers a correspondingly high level of immunity. It would be of great interest to test the ability of children in the acute state of the disease to manufacture antibodies in response to injected antigens, and to correlate the ability with the level of the globulin fractions in the serum; the tests would, of course, then be repeated in the children after they had been treated by the best available methods. It might be found that antibody production depended not merely on the level of γ-globulin, but on the level of some other protein fraction as well. The investigation might at least indicate some reason for the relative infrequency of streptococcal infections in African children; such infections might conceivably be modified in the presence of a large amount (or proportion) of γ-globulin, although other infections were not.

The high level of the blood urea during treatment was related to the amount of protein in the diet, and it was noticed that if the amount was kept below about 50 g. daily, the level of urea seldom rose above 30 mg./100 ml. In some cases, however, even 50 g. protein gave rise to abnormal increases in the blood urea, and it seemed that the usual mechanism for the regulation of the level was liable to failure. There is little in the histological appearance of the kidney to suggest any condition known to be associated with nitrogen retention, but it is obvious that kidney function must be carefully investigated before any conclusion can be drawn. The slight albuminuria of kwashiorkor (p. 105) which is the only other detail of evidence for a renal lesion, presumably represents increased permeability; since it is not accompanied by the passage of red blood cells or casts it must be akin to the transient albuminuria which occurs sometimes during fever, and in other conditions. The study of kidney function should be as comprehensive as possible.

The home diets of the children could have contained very little cholesterol, ground nuts (peanuts) being the only discernible source which might have contributed to any considerable extent. The hospital diets were almost fat-free during the period when the biochemical changes were being investigated, and must have been poor sources of ready-formed cholesterol. Nevertheless, there were large rises in the total cholesterol in the serum, and the most likely explanation is that rapid synthesis was occurring. This synthesis may have been from acetate, itself derived from various amino acids, and may have occurred intra- or extra-hepatically: determination of the chief sites of synthesis, and the way they are affected in the acute stage of the disease, would be enlightening. If cholesterol is a precursor of adrenal cortical hormones, and other steroid hormones, as appears likely from recent work, the study of choleserol metabolism may lead to an understanding of water retention 1 kwashiorkor, as well as of some of the endocrine peculiarities of fricans.

The recovery of enzymic activity in the serum and the duodenal uice was probably only a small indication of many changes which ere occurring at the same time. Of the enzymes measured, all xcept alkaline phosphatase increased in activity from the beginning of treatment ; this result may be accounted for by the fact that series of enzymes, and not a single enzyme, is measured by the nethod employed : the members of the series may have been affected 1 different degrees. The activity of other enzymes may not decrease r increase during treatment. The results obtained for tissue analysis y Waterlow (1951b ; see Table 16) showed that cytochrome oxidase nd lactic dehydrogenase were not, apparently, reduced in his cases 1 the acute phase of the disease, whereas cholinesterase was reduced. he oxidase and dehydrogenase do not require thiol (—SH) groups r their activation, and in this respect differ from cholinesterase, ancreatic esterase and lipase, and (probably) amylase—all of them nzymes which in kwashiorkor show reductions in their activity. he possible implications of this observation, and the role that ight be played by the failure of diets to supply sulphur-containing eactive groups, was discussed by Bigwood and Adriaens (1952 *Proc.*) nd by Dean (1952 *Proc.* a). Waterlow has recently given a full ccount of the methods of analysis he has used (Waterlow, 1953).

(*d*) *Summary and discussion of the biochemical changes.* The outanding changes caused by the severe form of the disease seen in ampala, which have so far been determined, seem to be a fall in e serum albumen, a high ratio of free to total cholesterol in the rum and low levels of serum amylase and esterase. Accomnying these changes are low levels of duodenal enzyme activity, fecting amylase, lipase and trypsin, and low absorption of dietary trogen and fat. Each of the changes can occur in other diseases, it all the changes probably never occur simultaneously except in vashiorkor.

There is no conflict between the results of investigations of athological anatomy, of biochemistry or of the response to treatent ; they all point towards defects of protein metabolism. No ise pathologist would maintain at the present time that the list of gans showing even visible changes in kwashiorkor is complete, physiologist could be satisfied with the meagre data about

TABLE 16

Enzyme activity of liver tissue and plasma in Gambian children before and after treatment

(*From Waterlow*, 1951b)

	Before treatment					After treatment					Normal values*
	Patient 232	Patient 229	Patient 203	Patient 250	Patient 235	Patient 232	Patient 229	Patient 203	Patient 250	Patient 235	
Plasma cholinesterase (cu. mm. CO$_2$/ml./minute)	25·0	23·2	27·8	34·5	38·8	—	53·2	58·7	42·9	60·0	60·0
Liver cholinesterase (cu. mm. CO$_2$ mg. dry weight/hour)	1·0	2·6	4·5	5·1	6·9	—	6·2	10·2	7·8	8·4	9·4
Liver lactic dehydrogenase (cu. mm. O$_2$/mg. dry weight/hour	10·5	10·3	—	3·6	7·7	—	5·8	6·2	7·8	5·6	5·9
Liver cytochrome oxidase (cu. mm. O$_2$/mg. dry weight/hour)	13·6	9·9	20·2	—	10·4	—	13·5	20·1	—	17·1	16·3
Fat (percentage on dry weight of liver)	34·5	—	—	20·5	17·9	—	5·0	15·6	11·3	12·4	12·6

Clinical conditions: Patient Nos. 232, 229 and 203 had oedema. No. 232 died. No. 229 was improved by treatment, and No. 203 made a good recovery. Patient Nos. 250 and 235 had no oedema; No. 250 was more severely malnourished than No. 235.

* Obtained from 11 children who were not badly nourished.

isturbance of function which are now available, and no biochemist ould pretend that the studies so far made of the changes in the erum or the duodenal juice or the tissues are adequate to describe hat is happening throughout the body. It would seem to be of econdary importance, however, to complete the list of organs, or describe all the changes in function and in various body sub-tances, unless by so doing the fundamental defect, or series of efects, can be uncovered. The hypothesis advanced (p. 223) to xplain enzyme failures in kwashiorkor may be proved wrong, but ther hypotheses capable of wide application to the known facts will o doubt be advanced as time goes on and knowledge deepens, and ne best hypothesis will side-track a great deal of interesting, but omparatively unimportant, discovery.

The existence, or possible existence, of variations in kwashiorkor . 37) underlines the necessity for objective criteria by which the isease might be described. The objective criteria so far obtained nay be considered scanty and not conclusive, but a reasonably trong case could be made out for the use in diagnosis of some of ne biochemical changes which appear to be found consistently. nly when the biochemical tests—or other tests, if they can be ound and established—have been applied in the different countries here kwashiorkor flourishes, will it be possible to speak with ertainty of true variations, and to sort out the fundamental differ-nces and similarities. The findings in one country must never be pplied without trial in another country; if that is done, the gnificance of differences due to different basic diets, to climate nd to weaning habits—to name only a few of the possibilities—will ways be missed. It may seem unnecessary to stress this obvious oint: lamentably, experience has already shown the necessity. he case is known of a refusal to repeat work done in Kampala ecause the repetitions seemed unnecessary, despite all attempts to now that the validity of the Kampala results is necessarily limited, an unknown extent, to the set of children and circumstances found ere. It is true that, at some time in the future, the wider validity the Kampala findings may become apparent: but that time is t yet upon us.

The completeness of recovery

Nothing is known about the completeness of recovery from vere kwashiorkor. In perhaps a year—the exact period depending on the intensity and nature of treatment—all the clinical signs ma be lost, and growth may be satisfactory, but the extent of the residu damage, if there is any, has never been proved. It will be of grea interest if at some time in the future, the exact course of a fe children can be determined. A study of the chemical changes wi be needed, and it is possible that some abnormality, such as th elevation of the γ-globulins which appears to be a somewhat con sistent African finding, will be disclosed. The starting-point of ful recovery might be taken as the attainment of the serum levels fo various constituents, found in children who have no history o kwashiorkor. Values for the serum of a few such children are give in Table 17 (p. 230). A reliable index of recovery that could b applied objectively would be a great advantage. The assessmen of nutritional status is at any time difficult : various measures hav been devised, and a thoughtful summary of many of them has bee given by Sinclair (1950), but it seems likely that the changes foun in kwashiorkor, which are not *in toto* those found in any othe disease, will need to be pursued in new ways.

4. Relapses, and the results of follow-up examinations

The early writers on kwashiorkor stressed the rarity of relapses (Castellanos, 1935) and this seemed to be an important point of distinction from classical pellagra, which at least in adults tends to reappear year after year. The return of oedema shortly after it has once disappeared, reported by Clark (1951a), should probably be classified with the increasing oedema seen by Janssen and le Roux : the most likely cause was imperfect treatment rather than a true relapse. The oedema may occasionally return long after the child is discharged from hospital, if the home diet is extremely unsuitable.

At Kampala, parents are urged to bring their children back a month after they have been discharged from hospital, but seldom do so. The children who have been seen after one month, and a few others who have been seen after several months, have all looked surprisingly well, even if still underweight, considering that it is usually obvious from the statements of the parents that they have been able to give the children very little extra protein-rich food. In recent years few children who have been given a full course of treatment at Mulago hospital have had to be readmitted for a return of kwashiorkor. Such an observation may, however, have little ignificance as the conditions of follow-up and after-care remain nsatisfactory.

Elsewhere very few follow-up studies have been reported. One hild who had had "a satisfactory diet in an institution during the welve months since his original discharge from hospital" was found y Anderson and Altmann (1951) to have low serum albumen and a igh γ-globulin, which suggested a continuation of liver damage. ltmann (1950) followed up 18 other cases for one or two years and ound them all to be in good health. Nearly all, however, showed ome evidence suggestive of imperfect recovery of the liver; in 6 of hem liver biopsy showed abnormal cellular reaction in the portal racts. There was no obvious excess of fibrous tissue or any vidence of cirrhosis.

The follow-up reported by Véghelyi (1950a) was startling, at east as regards children who had been oedematous. He was able o trace 36 such children whom he had treated approximately hree and a half years before (see p. 69). Only 3 were alive and ell, and even they had grown poorly. The other 33 had died, he cause of death being upper respiratory infection in 9, intestinal nfection in 12, "atrophy" in 3, tuberculosis in 2, accident in 1, nd unknown in 6. Post-mortem examinations had shown a fine irrhosis of the liver and pancreatic fibrosis. It should be borne in ind that Véghelyi's cases occurred during a siege when there was n acute shortage of milk and that conditions remained unsatisactory for a long time. It is probable that cases were inadeuately treated both during their stay in hospital and after their ischarge.

Brock (1953, personal communication) was able to report a very ifferent experience in a follow-up of about twenty cases of kwashirkor among Cape Coloured infants. These infants were treated r a long period in hospital at Cape Town and subsequently eceived an improved diet of European type. A biopsy performed wo or three years after the children had been discharged from ospital revealed no abnormality in the liver.

On the basis of this somewhat conflicting evidence it would ppear that relapse, or failure to make a full recovery, depends on e adequacy of treatment by diet in hospital and on the diet afterards at home. If the home diet is very unsatisfactory a relapse the severe illness may occur, but it is indeed very difficult to xplain why relapses appear to be so infrequent in some places.

They are fairly common in Guatemala City (Behar, 1953, personal communication).

Another problem remains to be discussed—that of the fate of the cases of mild kwashiorkor, which far outnumber the severe cases. The large majority never develop the typical signs of the advanced illness, and there have been few studies of the subsequent development. They probably remain underweight, even if yearly gains of weight are often within the normal range (Welbourn, 1951). Their hair is usually dyspigmented, but recovers in later childhood. Whether some organs are permanently affected, and whether any of the changes found in adult life reflect various aspects of chronic protein malnutrition is discussed in the last chapter of this book (p. 268).

5. The "nutritional recovery syndrome", and steatorrhoea during convalescence

Gomez, Galvan and Muñoz (1952) reported an interesting sequence of events which they observed in children who were being treated for kwashiorkor with a diet that contained about 56 g. protein, 48 g. fat and 175 g. carbohydrate. Of the 34 children described, 28 were aged between 2 and 5 years.

The progress of the children was followed by estimations of serum proteins and by serial liver biopsies. After 20 to 40 days' treatment, it was found that there was considerable liver enlargement, although the amount of fat in the liver was reduced; in sections of the biopsy specimens, the picture was dominated by "protein depletion images", and not by fat. The abdomen was distended and there was intrahepatic hypertension with the establishment of thoraco-abdominal venous anastomoses and the production of ascites. The total serum proteins increased, and there was a large rise in the amount of γ-globulin. The condition, which was called the "nutritional recovery syndrome", lasted about a month, and then the signs disappeared. It seemed to be alarming, but benign. It could not be explained, but the cause presumably lay in some quality of the diet used for treatment; variation of the diet would therefore seem to be the best means for the investigation of the syndrome. Gomez (1953, personal communication) now thinks that it occurs in all his cases that are treated for a sufficiently long period, but it has not been seen in Kampala and it has not been reported from other centres. It would be satisfactory to know, not erely that it had not been noticed in those centres, but had been finitely shown not to occur there.

The children who were submitted to duodenal intubation by arvalho, Schmidt and Pinto (1947; see above, p. 169), during nvalescence from kwashiorkor were said to have developed a ndition which resembled in some ways coeliac disease. They had racious appetites but remained thin; their stools were pale, bulky d offensive, and were thought to show evidence of a steatorrhoea which abnormalities of the faecal flora in the gut had con-buted. In 5 of 6 children who were given diets that contained tween 24 and 50 g. fat each day, the faecal fat, and the proportion unsplit fat, were within normal limits, although the level of the iodenal enzymes was low. It is possible that some unrecorded etary indiscretion was responsible for these somewhat puzzling idings.

THE RELATION BETWEEN SERUM VALUES IN KWASHIORKOR AND THOSE IN OTHER DISEASES

When the paper was written in which details were given of the ochemical investigation of the Kampala children, it was uncertain the results could be used as evidence for or against the theory that e disease was due to a protein deficiency, or to provide a set of sts suitable for recommendation for diagnosis, or indeed for any rpose except, possibly, the following of the course of the indi-lual child. The uncertainty was chiefly due to the absence of ta obtained from children who were similar in race, age, and neral living conditions, but who did not exhibit the usual signs kwashiorkor. It was subsequently found possible to obtain data a few children who satisfied these criteria, and the results are own in Table 17.

It must be admitted that the data are too few for entirely definite nclusions, but they appear to confirm that the changes found in ashiorkor, if taken together, are almost if not entirely diagnostic that condition. The changes in kwashiorkor are of a nature that ght reasonably be expected to follow a period of protein mal-trition: they do not offer much evidence for the exact nature of defect—whether a specific amino acid or a group of these acids nvolved, or whether the important factor is a substance (such vitamin B_{12}) which accompanies the proteins that have the

TABLE 17

Serum chemistry in kwashiorkor and in other conditions *

(*All values for* 100 *ml. serum*)

Number	Age (months)	Reason for admission to hospital	Protein				Urea mg.	Cholesterol			Esterase units	Amylase units
			Total g.	Albumen g.	Globulin g.	A/G ratio		Total mg.	Free mg.	Ratio		
N2	30	Fever and vomiting	6·03	3·50	2·53	1·38	—	56	34	0·60	45·6	61
N3	18	Fever and cough	6·40	3·67	2·73	1·34	17·5	125	45	0·36	50·0	94
N7	18	,, ,, ,,	6·68	3·60	3·08	1·17	14·4	98	73	0·75	43·0	85
N10	18	,, ,, ,,	5·72	2·94	2·78	1·06	18·4	146	49	0·34	32·7	94
N12	18	,, ,, ,,	7·12	—	—	—	—	108	50	0·46	—	43
N6	14	Fever and cough and diarrhoea	6·53	—	—	—	21·0	—	—	—	43·6	25
N1	36	Abscess on arm	6·70	3·43	3·27	1·05	14·6	125	40	0·32	50·0	107
N8	36 ?	Second-degree burn	7·67	3·41	4·26	0·80	10·3	155	51	0·33	49·0	94
N9	36	Polio	6·90	3·70	3·20	1·05	13·6	150	49	0·33	—	133
		Kwashiorkor : †										
		on admission	3·98	1·51	2·44	0·67	16·2	87	66	0·76	16·8	25
		after treatment	7·00	3·50	3·50	1·00	50·0	140	56	0·40	43·0	100

* From Dean and Schwartz (in the press).

† From Dean and Schwartz (1953).

ighest biological value, but they may perhaps serve to direct the earch for causative factors along some lines, and away from others. t seems fairly certain, for instance, that they lead away from any nown disease due to vitamin deficiency. The possibility that washiorkor is related to a deficiency of vitamin B_{12} awaits experi-nental proof.

At Kampala, it is unusual to find even in the serum of children ho have made the most excellent recovery, judging by the clinical igns, albumen globulin ratios that much exceed unity. Ratios veraging 0·92 were found by Dr. M. D. Thompson (1953; un-ublished results) in sera that she analysed by paper electrophoresis. y European and American standards this is a very low ratio, but it almost the same as that found by Lubschez (1948) in American hildren, who cannot possibly have had kwashiorkor, shortly after ey had had an infective illness. The globulin fractions were also milar. The mean Kampala values were 13·5 per cent α-globulin, 1·4 per cent β-globulin and 27·8 per cent γ-globulin. The mean gures found by Lubschez were 18·0 per cent α-globulin, 12·8 per ent β-globulin and 21·7 per cent γ-globulin.[1] The Kampala ildren would have been very exceptional if they had ever passed ore than a few months of their lives without an infection of some nd; however healthy they may be, almost all the children in the strict seem to acquire some infection every few weeks. It would of great value to know what levels of serum protein, and especially globulin, might be reached by Kampala children, given a full diet, ho were fully protected against infection.

The effect of infection on a child recovering from kwashiorkor as beautifully illustrated by Close (1953). As a result of treatment, e serum albumen rose in 7 weeks from 1·05 to 3·58 g./100 ml. and β and γ-globulins changed from 1·04, 0·57 and 1·13 g./100 ml. 0·91, 0·71 and 1·45 g./100 ml. The child then had an attack typhoid fever: the albumen fell to 1·59 g./100 ml. and the α, and γ-globulins rose to 1·11, 0·89 and 2·55 g./100 ml. The anges in the albumen and the γ-globulin are striking, and clearly ow that the interpretation of "abnormal" values found in cases of ashiorkor is not a simple matter.

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[1] Includes θ and γ-globulin fractions.

THE PREVENTION OF KWASHIORKOR

If the theory of the aetiology of kwashiorkor advanced in thi book is accepted, it will follow logically that a policy of preventio will aim at increasing the amount of protein available to children i the years when they are most susceptible to the disease. The communities to be dealt with are mostly culturally retarded, and th methods to be employed will have to be adapted to their particula levels of education and understanding. The obvious problems i agriculture and animal husbandry are not necessarily the ones tha should be tackled first.

1. Education

The education of doctors and their staffs in the recognition o the disease is of prime importance. Because kwashiorkor has no been common in European and North American countries, where a large proportion of the world's doctors have been trained, it has been usual for tropical hospitals to be staffed with doctors who have never heard of it, or think of it as one more exotic disease with a meaningless name. This situation will improve as more of the standard text-books admit the disease to their canon, but it is notorious that text-books follow years behind advancing knowledge, and it is to be hoped that all courses of teaching in tropical medicine will include an adequate account of the subject. Since diagnosis depends in practice on seeing as well as believing, it would undoubtedly be a great advantage if children showing the acute manifestations of the disease could be taken to training centres, by air if necessary; as demonstrations they would be worth many times their weight in text-books.

Together with accelerated education of the medical and nursing professions must go education of the public. Many African tribes recognize the disease and have a name for it (p. 283). Too many of them seem to believe that it is an inevitable accompaniment of a certain period of childhood, and not the kind of illness for which a child should be taken to a hospital or dispensary. An element of shame is often present in the mother's mind and may cause her to hide the child away; she must be given convincing evidence of the value of early treatment. Education must use all the means which can be brought to bear: films, posters and other visual aids, newspapers and advertisements in the towns and oral propaganda in the country, must be used as circumstances direct. In schools where hygiene is taught, something of the disease should be explained, along with a few simple facts about nutrition in general. The establishment of ante-natal and child welfare clinics should provide a ready means of applying instruction where it is most needed—in the mind of the mother when her attention is being focused on the well-being of her child.

Education must reach all the communities, and all their levels. In a country such as Uganda, where it is usual for an African servant to bring his wife and family to his master's house to live, it is not unreasonable to expect the master or mistress of the household to be able to recognize the disease. The employers of large bodies of African labour should also be urged to keep an active look-out for ts early signs. To a large extent, of course, kwashiorkor is a disease of poverty and poor social conditions, and improvement in health must wait upon social improvements, but there is an urgent need in many places for a short-circuiting of the usual leisurely train of events. The example of Britain may be borne in mind. Various reports—those of Orr (1928) and Widdowson (1947), for instance, have made it clear that the amount of protein, and especially animal protein, consumed before the recent war rose with income and social standing, and the cheap distribution of milk to children, instituted before the war and carried on all through it, was probably the most mportant single factor in redressing the inequality.

The advice given to mothers must be carefully calculated to ccord, not only with their degree of understanding, but with their bility to buy, or to acquire in other ways, the needed dietary supplements. It was held for a long time that undernutrition of he mother had no effect, unless it was extreme, on the size of her unborn child or on her ability to lactate. It is now known that both of these may be affected by even a moderate degree of undernutrition Dean, 1951) and some evidence has been produced that human milk may be more variable in composition than was once thought o be likely. If the reports of Auffret and Tanguy (1949) are substantiated, it may be found that the milk is, in certain circumstances, acking in some of the amino acids possibly of particular importance in the cure, and also in the prevention, of kwashiorkor. A good case could therefore be made out for starting the dietary improvement of a community by improving the nutrition of the mother during pregnancy. This may be a counsel of perfection difficult to follow, and it may be more expedient to start at some later epoch in the li of the child, but it is worth bearing in mind that the ideal sup plementary food would be one which was suitable for use at all ages The acceptability of cow's milk as such a food is growing throughou the world, and the improvement of nutrition is nearly always con sidered in terms of the possibility of introducing milk, in one form or another, into the diet.

2. The encouragement of breast feeding

Despite the fact that it may sometimes be possible to detect some impairment in the quality of breast milk there is no doubt that breast feeding must be encouraged, and everything possible done to prevent retarded communities from following the example of those more advanced ones in which ability to lactate seems to be fast declining. The decline may be as much a psychological as a physiological phenomenon ; a certain serenity of mind seems to be conducive to good lactation, and a growing disturbance of that serenity is to be feared as much as the spread of the more spectacular diseases of civilization. Kwashiorkor is not at present a disease of the first six months of life for the simple reason that breast milk is adequate and protective ; it will be seen earlier and earlier if breast feeding fails.

Although the frequency with which a child can be seen at the breast at the age of 2 or 3 years can be misleading (p. 51), there is little doubt that small amounts of milk are better than none. In backward communities breast feeding may often continue profitably well into the second year. Weaning as a natural event occurs not because the supply of milk suddenly stops, but because the human capacity to lactate seems to be adjusted to the full provision of the child's needs only for a limited time. It is only exceptionally that the mother has enough milk to satisfy all the demands of growth of a healthy child, whatever the race, for more than four to five months. What happens after that time is fundamental to the study of kwashiorkor. Every effort should be made to continue breast feeding as long as possible, the only definite contra-indication being the unmistakable signs of another pregnancy. It is often feared, especially by European doctors and nurses, that prolonged lactation will be a strain on the mother, but the fear seems to have little foundation of fact. If at eighteen months the mother is producing half a litre of milk daily, she will be supplying about 7 g. protein—about onehird of the protein requirements of the child at that age—and this ig gain to the child represents only a small loss from the mother. reast feeding should not be abandoned because the mother thinks he has little milk. Premature weaning (and there is no other word or it in the biological sense) should be allowed in the first year of life nly to those whose economic circumstances, education and skill llow them to give a pint of clean cow's milk each day to each child.

Among culturally retarded groups a continuation of breast eeding has one great disadvantage: it tends to delay the beginning f mixed feeding. Both mother and child find it easier to wait ntil the second year and the child may suffer from a mild degree f general undernutrition if the milk is not superabundant. From he fourth month mixed feeding should be introduced, and it is ssential that the mother should offer the other food before she ffers the breast. The choice of suitable food is usually wider than s recognized; many foods taken by adults can be given to young hildren mashed or ground, or with milk or gravy. An effort should e made to get children more than 6 to 8 months old to take almost ll articles of the adult diet at two or three meals a day, and to estrict breast feeding to times not covered by those meals. There s a regrettable tendency to omit meat, fish, beans and peas from he infant's diet, because they are often tough, but adequate methods f preparation, needing only the simplest tools, can usually be learnt.

3. Improving the transitional diet

The various means which have been adopted for making the ransition from breast milk to an adult diet have been discussed in ull elsewhere (Dean, 1953). Ideally, the transition would be ased on the introduction of cow's milk into the diet. For many easons, it is necessary to consider here the other possibilities. The bolition of tsetse fly, the control of cattle disease, the improvement f pasture, and the improvement of the yield of local cattle, may one lay enable all children to receive some cow's milk, but that day is ar in the future.

In spite of a certain amount of evidence to the contrary, there s still a widespread tendency to accept without question the idea hat animal protein must be higher in nutritional value than protein rom any other source. Some discussion of this idea, and of the eculiarities of foods grown extensively in countries where kwashi-rkor is common, may not be out of place.

T

Amounts of protein, fat and carbohy

Food	Amounts, in 100 g. of					
	Protein g.	Fat g.	Carbo-hydrate g.	Calories	Arginine	H
Milk, cow's, fresh	3·1	3·5	4·6	62	4·3	
,, ,, †skimmed, dried	35·6	1·0	52·0	360		
,, human	1·0	4·5	7·1	75	4·3	
Fish *	17·0	3·0	Trace	95	7·4	
Egg, whole	13·0	11·0	0·9	153	6·4	
Bambara ground nut (*Voandzia subterranea*)	18·0	6·0	55·0	346		
Banana (sweet : *Musa sapientum*)	1·0	0·3	24·0	103		
Cassava flour	1·5	Trace	77·0	314		
,, fresh	0·7	Trace	32·0	131		
Chick pea (*Cicer arieninum*)	22·0	5·0	55·0	353		
Coconut kernel	4·0	40·0	7·0	404		
Cottonseed					7·4	2
Cow pea (*Vigna unguiculata*)	24·0	1·0	44·0	281		
Groundnuts (peanuts)	23·0	47·0	10·0	555	9·9	2
Lentil (*Lens esculenta*)	24·0	1·0	50·0	305		
Linseed					8·4	1·
Lucerne (alfalfa)					4·3	2·
Maize germ	8·0	5·0	43·0	249	8·1	2·
,, whole	10·0	4·5	67·0	349	4·8	2·
Millet (*Pennisetum typhoides*)	11·0	5·0	69·0	365		
,, (*Eleusine coracana*)	6·0	2·0	74·0	338		
Oats, rolled	12·0	8·7	65·0	386	6·0	2·
Peas (garden)	22·0	1·0	53·0	309	8·9	1·
Plantains (*Musa balbisiana*)	1·0	0·3	24·0	103		
Potato (sweet : *Ipomoea batatas*)	2·0	1·0	26·0	121		
Rice, white	7·0	1·0	78·0	349	7·2	1·
Rye, whole	8·0	2·5	68·0	327	4·3	1·
Sesame seed	20·0	50·0	10·0	570	9·2	1·
Sorghum (*Sorghum spp.*)	10·4	3·4	70·9	356		
Soya bean	35·0	18·0	20·0	382	7·1	2·3
Sunflower seed	27·0	45·0	14·0	569	8·2	1·7
Taro	2·0	Trace	20·0	88		
Wheat germ					6·0	2·5
,, whole	11·5	2·4	62·0	316	4·2	2·1
Yam	2·0	Trace	23·0	100		
Yeast	40–50	—	—	—	4·3	2·8

[1] From Platt (1945), whose values are for *edible* portions.
[2] From Block and Mitchell (1946–47).

The amino acid composition of various animal and vegetable proteins is given in Table 18. There is very little difference between animal proteins in respect of essential amino acids ; they all contain large amounts of total sulphur-amino acids (cystine *plus* methionine) of lysine, tryptophan, and arginine. It is probable that too much has been made in the past of various estimates of 'optimum' *f various amino acids,[2] in foods*

Amounts of amino acids (g. amino acid per 16·0 g. nitrogen)

Tyrosine	Trypto-phan	Phenyl-alanine	Cystine	Methio-nine	Threo-nine	Leucine	*Iso*-leucine	Valine
5·3	1·6	5·7	1·0	3·4	4·5	11·3	8·5	8·4
5·2	1·9	5·6	3·4	2·2	4·6	9·8	7·5	8·8
4·4	1·3	4·5	1·2	3·5	4·5	7·1	6·0	5·8
4·5	1·5	6·3	2·4	4·1	4·9	9·2	8·0	7·3
3·2	1·4	6·8	2·0	2·1	3·0	5·0	3·4	3·7
4·4	1·0	5·4	1·6	1·3	1·5	7·0	3·0	8·0
5·1	1·5	5·6	1·9	2·3	5·1	7·0	4·0	7·0
5·7	1·6	4·5	1·6	2·3	3·3	6·6	3·6	4·4
6·7	1·3	5·5	1·8	1·6	4·7	13·0	4·0	6·0
5·5	0·8	5·0	1·5	3·1	3·7	22·0	4·0	5·0
4·6	1·2	6·6	1·8	2·4	3·5	8·3	5·6	6·3
—	0·7	4·8	1·2	1·0	3·9	6·4	4·1	4·0
5·6	1·3	6·7	1·4	3·4	4·1	9·0	5·3	6·3
—	1·3	5·6	—	1·3	3·0	6·2	4·0	5·0
4·3	1·9	8·3	1·3	3·1	3·6	7·5	4·8	5·1
4·1	1·2	5·7	1·9	2·0	4·0	6·6	4·7	4·2
2·6	1·3	5·4	1·3	3·4	4·0	6·2	5·2	5·2
3·8	1·0	4·2	0·8	—	3·8	6·7		—
4·4	1·2	5·7	1·8	2·5	3·3	6·8	3·6	4·5
3·6	1·3	4·1	1·0	1·9	5·5	7·4	5·9	5·0

* Values for protein, fat and carbohydrate are those for fresh-lake fish ; the alues for dried fish of the same kind are about three times higher. Values for nino acids are for fish *meal.* † From Dean (1953).

equirements of essential amino acids, but there is little doubt that iets which include a fair proportion of animal protein are less likely cause deficiency states than purely vegetarian diets. It is however possible, by choosing a suitable mixture of plant proteins, to pproximate roughly to the mixture found in animal proteins, and has been shown that healthy children can be fed satisfactorily on all-plant diets (Dean, 1953). In devising such diets, the greatest difficulty is found in providing enough lysine and methionine, as most plant proteins do not contain large amounts of these amino acids.

Animal protein is accompanied by vitamin B_{12} and some other substances, at present imperfectly identified, which appear to enhance the growth of experimental animals and are almost certainly needed for the optimum growth of man. The vitamin and its companions are sometimes referred to under the generic name of the ' Animal Protein Factor ' ; the name emphasizes the usual natural source, but is now considered unsatisfactory because the ' Factor ' can be produced by various bacteria and moulds. It has recently been discovered that vitamin B_{12} must be classed amongst the ' lipotrophic ' substances ; that is, the substances which help to mobilize fat deposited in the liver (p. 181).

The catalogue of the virtues of animal protein is even then not complete. The protein is usually found in association with small amounts of carbohydrate and considerable quantities of fat. In contradistinction, plant protein is almost always associated with large amounts of carbohydrate, and only occasionally, as in some of the beans and nuts and a few seeds, with much fat. The absence of fat from a child's diet is not usually, of itself, a great disadvantage, but the caloric value of fat is more than twice that of carbohydrate, so that the omission of fat invariably leads to a large increase in the bulk of the diet if the caloric value is to be maintained. The superior value of meat, milk, and other foods which contain animal protein is sometimes expressed by the use of the ratio of protein calories to total calories, or the ratio of protein (g.) to 100 calories (Table 19). The latter ratio is of considerable importance because food is usually consumed until hunger is appeased. The total calorie intake may appear adequate, but the amount of protein taken depends on the protein/calorie ratio. The ratio is usually higher in animal foods than in plant foods. Among the latter there are roughly three classes : leguminous seeds (beans and peas), and nuts which have a high protein/calorie ratio ; cereal seeds which have a moderate ratio ; and vegetable storage organs, which have a low ratio.

It is obvious from Table 19 that foods such as cassava, sweet potatoes and plantains are much poorer in protein than any of the cereals. Meals of them are usually so bulky that a small child cannot eat enough to satisfy his protein requirements. There is no need to consider the replacement of the carbohydrate of the foods—the carbohydrate of the otherwise despicable banana may be, in its right place, excellent—and fat can probably be left out of the argument. By what means can the protein content of the diet be improved?

The essence of the problem is to provide 40 to 50 g. protein which will adequately supplement the 10 to 15 g. protein of the home diet. It can be seen from Table 11 that small quantities of fish or meat, or of soya beans, slightly larger quantities of other beans, peas or groundnuts, and larger amounts of any of the cereals, would be needed. Prices vary from place to place, but with the exception of fish, which may in some districts be very cheap, the animal proteins are too expensive for wide use in amounts which might be of real value to the child. In Uganda even fish is too expensive to be used more than occasionally. There is no large African fishing industry. It might be possible to obtain small quantities of fish if the European-run fishing industry were greatly expanded, or if pond culture were introduced on a large scale, but any such prospects belong to the fairly uncertain future. Even if he fish were available, there would remain the necessity of finding he best ways of processing it so that it was suitable for infant feeding.

TABLE 19

Ratio of protein (g.) to 100 *calories in various foods*
(*Data from Brock and Autret*, 1952)

Food	Ratio
Cassava	0·83
Cooked bananas (plantains)	1·0
Sweet potatoes (*Ipomoea batatas*)	1·1
Rice (white, milled)	1·7
Taros	1·7
Millet (*Eleusine coracana*)	2·0
Rice (home-pounded)	2·0
Yams	2·3
Maize (whole-meal)	2·6
Millet (*Setaria italica*)	2·9
Sorghum (*Sorghum vulgare*)	2·9
Wheat flour (medium extraction)	3·3
Millet (*Pennisetum glaucum*)	3·4
Groundnuts (peanuts)	4·7
Cow's milk (3·5 per cent fat)	5·4
Bambara ground nuts (*Voandzia subterranea*)	5·7
Beans and peas	6·4
Beef (thin)	9·6
Cow's milk, skimmed	10·0
Soya bean	11·3
Fish, fatty	11·4
,, dried	15·4

Uganda is not exceptional amongst tropical countries in that the supply of milk is poor, and is unlikely to be much increased in the near future. In Uganda, therefore, and the Protectorate is probably typical in this respect of many countries, there seems to be little hope that animal protein will in the near future be available in large quantities, and at sufficiently low prices, to form a popular supplement to the diets of small children. Plant proteins, in one form or another, must take their place. The use of soya has already been described. Groundnuts are the only other high-protein food at present obtainable. They are fairly expensive, but are well known, well liked and available for most of the year because they store well. They are, however, short of methionine and are not easily digested. A good food might be made from residues left after the oil has been extracted, but research would be needed to find the best way. Of the cereals, maize is the only one which is to be found in large quantities all the year round. It is grown in Uganda and Kenya, but for the Ganda (the tribe inhabiting the district around Kampala) it is a food which is much disliked, and is only eaten if plantains, sweet potato or cassava are unobtainable. It also has the disadvantage that it takes up a great deal of water when it is cooked into a gruel : it takes up less when it is made into the more or less damp paste known by the Luo and other tribes as '*ugali*', but in that form it is less suitable for small children. It is easy to see how a Kampala family, having to buy a large proportion of its food because the family plot of land is so small, might be forced by economic stress and prejudice to live on a diet which would be inadequate for its small children.

The example of an urban family has been used because the drift to the towns is increasing in momentum in many parts of the world, and, if measures are not taken quickly, the towns are likely to be the main centres of kwashiorkor in the near future. New industries are being rapidly developed in Uganda, and in a few years a large part of the country's population will be living within a few miles of two, or possibly three, big towns. Inevitably, the amount of food each family will be able to grow at home will get smaller, and the amount that must be bought will increase. The children will suffer unless ways can be found of producing a cheap and acceptable high-protein food that can be added to the rest of the diet. It is hoped that in the next few years it will be possible to exploit for this purpose not only the foods already mentioned, but many others. For instance, sunflower-seed meal, "flours" made from beans, and cotton-seed meal deserve extensive trial, although there is much to learn about them.

It has been widely believed, and was certainly the opinion of the writer (R. F. A. D.), that plant protein materials, from a single plant or from combinations of plants, could be increased greatly in value if they were mixed with a protein of animal origin. There is no doubt that if plant protein materials are being dried, the addition of even a small amount of milk conveys great mechanical advantages. The nutritional advantages are less certain. Gomez and Galvan (1947) could not produce any large improvement in the growth of malnourished children by adding small amounts of animal protein to a vegetarian diet, and various recent feeding experiments, including some undertaken in Kampala, but so far unpublished, have seemed to show that additions of animal proteins, or of vitamin B_{12}, may not have the expected effect if given to children who have been living for a long time on diets low in total protein. The reasons are obscure. There may be a failure to respond to the added protein, or the additions may not have been sufficiently generous. On the other hand, the concept of protein deficiency may be in need of change. Until now, the emphasis has been on quality of protein, but in future it may have to be on quantity ; concentration on the importance of essential amino acids has obscured the plain fact of scarcity. Rough estimates of total protein in diets of people in underdeveloped areas have usually been much too high ; measurements (p. 61) are much lower. The healthy European child on a good mixed diet grows well if the total protein amounts to 60–80 g. daily : he might grow equally well if he had 80–100 g. protein exclusively from plant sources, the extra margin being added to compensate for the lower biological value, and perhaps availability, of the plant proteins. The child in primitive surroundings who develops kwashiorkor on a diet containing very little animal protein has not been taking 80 to 100 g. total protein each day, but an amount nearer to 15 to 20 g. It is fairly certain that kwashiorkor does not occur anywhere in the world if there is a high total protein intake ; the optimum animal protein intake for a growing child is still unknown, and its determination is tedious and difficult. For the prevention of kwashiorkor, it may be expedient, and may prove sounder, to concentrate on increasing total protein rather than one of the constituents.

Wherever the large-scale prevention of kwashiorkor is undertaken, it will be necessary to consider the manufacture of a food comprising locally-grown ingredients, in a form which will keep well under difficult climatic conditions. The foods available will naturally vary from place to place. In Kenya there is some milk available for drying, particularly in those seasons of the year when the pasture is at its best, and the dried mixture of skimmed milk and a cereal may prove to be a practical solution of many difficulties. A great deal will depend on the cost of processing: the cost of adding a small amount of milk—perhaps enough to make 10 per cent of the weight of the finished dry material—will be small and its advantages, from the point of view of ease of manufacture, whatever the added nutritive value, very great. In Uganda, where there is not much milk and where there is little prospect of the amount being increased in the near future, it seems probable that either soya or sunflower, or perhaps boiled or ground fish, will have to be incorporated with a cereal or with banana. The best methods of preparation will only be found after considerable research; laboratory and pilot plant investigation will be needed before manufacture can be considered, and every step must be controlled by tests with animals and children. There being no local tin-plate industry, the packing of the dried material will also demand careful investigation. Packets made from plastic tubing may be found satisfactory.

It is well known that the cost of industrial processes of food manufacture depends largely on the amount of money which has to be spent on research; the price of the final product is so calculated as to reimburse the manufacturer for his initial unproductive period. It may be necessary for the costs of research to be borne by the local Government, or by some other organization that does not demand the prospect of immediate profit. The actual manufacture could then be handed over to commercial enterprise if that were considered advisable. The abolition of kwashiorkor from a selected area, especially if it could be carried out in a short time, would be the best possible demonstration to an administration that its money was being well spent, and also the best way of enlisting popular support and enthusiasm. The advocates of such schemes are always met with the objection that it is unreasonable to expect people to change their food habits easily. The readiness with which mothers all over the world will spend money on tins of condensed and evaporated milk is itself an answer to this objection, and experience in the field shows that conservatism in the feeding of children can be broken down if demonstrations of the value of new foods are given convincingly. It is probably much sounder to try to introduce acceptable additions to existing diets rather than to try to insist on alterations in the diets by the omission of well-liked foods.

Most of what has been said so far applies only to a comparatively well-organized community, living close to possible centres of distribution, or having good communications with such centres. More undeveloped communities, such as may exist within a few miles of large towns if communications are exceptionally difficult, have very small experience in the buying of food. A little may be obtained by barter, but as a rule the greater part of the family's needs is supplied by the family's agricultural activities. The prevention of kwashiorkor in such communities cannot be made to depend entirely on the reluctant purchase of a strange food. It will be necessary to divert the peasant agriculture towards new crops which will supplement the old ones. Soya is a possible addition, although it demands conditions of climate and soil that are not everywhere available. It has the disadvantage of needing special preparation. The Chinese many centuries ago solved the difficulty in various ways, including the precipitation of a kind of curd from a suspension of the ground bean, and the Malayans use a fungus which acts on the damped beans and renders them digestible. Neither method is beyond the wit, the means, or the skill of the most imperfectly educated mother, but a great deal of propaganda would be needed before the methods could be introduced on a large scale, and the climate may not everywhere be suitable for the growth of the Malayan fungus. It would probably be more satisfactory to concentrate on increased planting of beans or peas, of sunflower, and of a suitable cereal. The problems of making preparations of these foods which would be suitable for small children do not seem to be so great, although some care is needed, particularly with beans, to make them easily digestible. On the Gold Coast, the following method is used for the preparation of a food for children from tigernuts (*Cyperus esculentus*, Linn.) and rice. The nuts are put into water, and any that float are removed, as they spoil the flavour. The remaining nuts are washed, drained and beaten well in a mortar. They are then mixed with water and strained through a cloth, mixed and strained again The rice is pounded or ground, added to the strainings, and boiled, a pinch of salt, and sometimes a little sugar, being added also. These details were supplied by Dr. M. Autret (1954, personal communication), who has also heard of a similar method used in the Ruanda-Urundi in Central Africa for making a " milk " from beans. There are undoubtedly variants used elsewhere, and many possibilities of the same kind that await exploration.

The magnitude of the task of increasing the protein supply of a rural community accustomed to use such foods as cassava or sweet potatoes as their staples, can be seen from Table 20. In Europe and the United States, the staple foods are cereals which have at least 8 to 10 per cent of protein. Many of the tropical staples have only 1·0 to 1·5 per cent protein, and the amount of supplementary protein that has to be supplied is comparatively enormous. For a given acreage a relatively large proportion of land must be converted from the usual staple to the high protein crop, the proportion being much greater than if the staple were, for instance, wheat. Much will depend on increasing yields to the utmost, by the choice of varieties of plants most suitable to the locality, and giving the maximum of protein, and by the use of fertilizers and other means for increasing the weight of the harvest.

TABLE 20

Yields per hectare of some plants grown in Africa
(*From Brock and Autret*, 1952)

Crop	Yield of protein kg.	Yield of total calories (millions)
Cassava flour	30·0	6·75
Sorghum	33·0	1·85
Sweet potatoes	36·5	3·10
Rice	42·3	2·15
Millet	44·0	1·53
Cassava (whole)	58·5	7·09
Maize	73·0	2·84
Yams	82·9	3·55
Beans or peas	88·8	1·38
Groundnuts	113·4	2·42
Soya beans	129·0	1·21

Finally, it is necessary to consider the possibility that supplies of various vitamins and minerals will have to be added to the children's diets. Enough has possibly been said in other parts of this book to indicate that lack of vitamins, with the possible exception of vitamin B_{12} and its associates, does not play a large part in the production of kwashiorkor. In some circumstances, however, it will be necessary to find sources of supply of the vitamins that are lacking. No general advice is possible, except that natural sources are nearly always to be found locally if they are carefully sought, and are always much cheaper than synthetic sources. With vitamin B_{12}, the position may be different ; there are probably no plant sources, and one reason for advocating the addition of a small amount of milk to a diet is that it brings a small, but probably adequate, amount of the vitamin. By-products of the manufacture of antibiotics, which are rich in vitamin B_{12}, are daily becoming cheaper ; they are being used in increasing amounts for the feeding of farm animals, and could probably be used after very little refinement in the feeding of children.

It is obvious that changes in the agricultural patterns employed by a community cannot be effected without the co-operation of a great number of administrative departments. The first step should probably be a survey, undertaken jointly by the medical and agricultural authorities of a district, with the object of finding out as exactly as possible the kind and amount of food which is grown at he various seasons of the year. Special attention should of course be given to the proteins of the food. The next step would be the selection by the agriculturists of those new foods which are the most suitable to the climate and the soil, bearing in mind the possibility or impossibility of local storage, as well as less tangible difficulties such as local prejudice. The final step—the introduction and encouragement of the new crops—would have to be carried out by he joint efforts of all the local administrators, including not only the technical advisors, but the District Commissioners (or their equivalent) and the chiefs. To some agricultural officers, the need for the co-operation of so many different departments may not be immediately apparent ; too often in the past they have been asked o devote their educational skill to the introduction of cash crops or a famine reserve, but most of them can be expected to welcome he opportunity of taking part in a co-ordinated plan, especially if he plan is mostly of their own devising.

It is extremely important to ensure that the stimulation of a demand for a new food does not out-run the possibility of satisfying hat demand. There may be well-meaning people who will make t their duty to try to introduce improved diets into backward communities, as soon as the smallest amount of work has shown how improvement might be brought about. The activities of such people ould perhaps be most advantageously utilized by making them a part of any new scheme of development, by asking them to be responsible for a project such as a limited trial in a specified area. The results of the stimulation of a demand that could not be met, or could be met only for a short time, at the end of which supplies failed, would be catastrophic. The free distribution of dried milk, started with the most generous of motives, may itself be ultimately dangerous if this principle is not understood. Any such distribution can only be a palliative measure, at best: it cannot be a permanent solution of the difficulties of feeding children well. The best solutions are those which can be worked out in the countries concerned, and within the economic and agricultural possibilities of those countries.

SUMMARY OF KWASHIORKOR IN CHILDREN

1. Kwashiorkor is most frequently seen in children who have recently been weaned: that is, in children between the ages of 1 and 2 years.

2. Lack of protein in the diet is probably an important cause. The lack may be due to poverty or to habits of growing and eating foods which supply adequate carbohydrate but little protein.

3. The clinical picture includes weight loss (with probably some failure of skeletal development), muscle wasting, oedema, changes in the hair and skin, anorexia, failure of digestion, and a mild anaemia. There is also apathy and misery.

4. All the clinical signs are not always present in any one case. The signs are found in varying degrees, and are not well correlated with the severity of the general condition; at Kampala, however, oedema, anorexia, and profound apathy, and a characteristic dermatosis, indicate a state that will be fatal if allowed to persist.

5. The mortality is very high if the correct treatment is not given. Some children die suddenly without apparent cause.

6. The most striking histopathological changes are found in the pancreas and the liver. The acinar cells of the pancreas atrophy, losing their zymogen granules: the liver is infiltrated with fat, which is deposited first at the periphery of the hepatic lobule. Many enzyme-secreting cells throughout the body are affected in the same way as those of the pancreas. Changes probably occur in all organs, especially in those which have a high rate of utilization of nitrogen.

7. In the serum, the total proteins are reduced because the albumen fraction is very low. There is a very high proportion of γ-globulin, but this may be due to infection, and not to kwashiorkor.

The total cholesterol is reduced, and there is only a small part of it in the combined form. The activity of serum esterase, amylase and pseudo-cholinesterase is low. Large amounts of anti-diuretic hormone appear to be circulating in the blood.

8. In the duodenal juice, the concentrations of amylase, lipase and trypsin are reduced to very low levels.

9. Some functions of the liver may be impaired, but to a smaller extent than might seem likely from a consideration of the extent of the fatty infiltration. Kidney function has not been tested fully, but in many cases there is a slight albuminuria.

Suprarenal function needs further investigation.

10. Treatment with pure vitamins and with lipotrophic substances fails to relieve the general condition unless large amounts of protein in an easily assimilated form are given at the same time.

Cow's milk is probably the most satisfactory source of the protein needed for treatment. It must be given in a concentrated form, accompanied by little lactose and less fat. A two-to-one mixture of dried skimmed milk (34 per cent protein) and calcium caseinate (80 per cent protein) gave good results at Kampala.

The exact nature of the factor(s) responsible for bringing about improvement in the children's condition has not been determined.

11. A mixture of plant proteins fortified with vitamin B_{12} has given good results in the treatment of a few cases, but has not supplanted milk.

12. Successful treatment brings about a rapid improvement in the general condition. Within a week, the oedema is lost, the skin begins to heal, the appetite improves and the demeanour becomes more normal. The hair does not recover its colour, but is finally replaced by hair of normal colour.

13. Treatment increases the amounts of serum albumen, cholesterol, non-specific esterase and cholinesterase. The pancreatic enzymes in the duodenal contents are restored to high activity.

The enzymes affected in the acute stage of the disease, and restored by treatment, may be those which require thiol (—SH) groups for their activation.

14. Treatment restores the acinar cells of the pancreas, and slowly removes the fat from the liver. The fat leaves first the parts of the lobule where it was latest deposited.

15. The completeness of recovery, and the ultimate prognosis, cannot at present be assessed. The connection between the fatty

condition of the liver in children with kwashiorkor, and the fibrotic states which are common in adult life, has not been fully established.

16. The prevention of kwashiorkor is an urgent problem. It is necessary to find ways in which the diets of children can be supplemented with large quantities of protein of high quality. The practice of premature weaning must be discouraged, the people must be educated into an understanding of the special dietary needs of the child at weaning, and new sources of protein must be found.

17. If neither milk nor any other source of animal protein can be made available, it will be necessary to use plant proteins. Mixtures from various plant sources can probably be produced in most countries, in forms that are suitable for children. The mixtures may need fortification with minerals and vitamins.

18. It is probable that many children suffer from a mild form of kwashiorkor. The condition cannot at present be accurately defined and needs much further investigation.

PART IV

PROTEIN MALNUTRITION IN ADULTS

The majority of the early investigators of kwashiorkor dealt with adults as well as children and considered that there was one disease which affected all age groups. Later the severity and the peculiarly heavy incidence of kwashiorkor in young children came to be recognized, and some workers regarded the disease as confined exclusively to infancy. To do so was reasonable as long as the enamel-paint dermatosis was regarded as the essential " hall-mark " of the disease (p. 23), for the dermatosis is very rare in adults. As the importance of the dermatosis receded the question of the identity of the condition in adults was re-opened.

For the time being the question of the continuation of the kwashiorkor of childhood into adult life must be left open. There is, however, a condition seen in adults in the Tropics which has some features in common with kwashiorkor and which appears to be due largely to protein deficiency. As with kwashiorkor, there is an acute phase in which the disease is serious and also a milder condition which is more difficult to define. The acute phase has received much more attention and a number of accounts which seem to be essentially similar can be found in the literature.

Some preliminary points must be mentioned before the question of protein malnutrition in adults can be properly discussed. Firstly, adults and children in the Tropics take the same diet ; if the infants suffer from protein malnutrition to a severe degree, adults also will be likely to suffer to some extent, although their protein requirements may be lower than those of infants and their tissues possibly less sensitive to a lack of protein. Secondly, the organs that bear the brunt of the attack of protein malnutrition in infancy will probably show abnormalities in adult life. Thirdly, adults who have previously been well fed, especially during the period of growth, and who sustain their first period of protein malnutrition in adult life must be very rare in the Tropics. In adults, therefore, the clinical appearance is likely to be confused, and the histopathology will show recent alterations grafted on to varying degrees of older damage.

Fourthly, infants who contract kwashiorkor after weaning have recently suffered a more or less abrupt transition from moderate affluence to poverty as regards their intake of protein, especially that of animal origin, whereas a sudden severe reduction of protein in the diet of the adult African is only likely to occur in unusual circumstances ; for instance, when he comes as an immigrant labourer to a large town, or when he is taken to a badly-run prison, or when he contracts a debilitating disease. The African is more prone to suffer from transient episodes of a moderate degree of protein malnutrition, which are not likely to cause obvious ill-health unless they are complicated by some other factor. The factor is often an infection, especially a chronic one such as tuberculosis, trypanosomiasis, amoebiasis, or anklyostomiasis, or any other chronic disease affecting the intestinal tract. In some of these conditions protein katabolism is increased by the febrile process, in others anorexia produces a severe deficiency of calories and the body may be living on itself, and in yet others the appetite may be retained but the diet is inadequate to meet even the slightest additional demand. If the infections are successfully treated many of the signs of protein malnutrition disappear. The presence of nutritional disease might not be suspected until it is realized that in well-fed persons none of the infections produces alterations in the hair, oedema, and undigested food in the stools, nor in well-fed persons who die of the infections is an atrophic pancreas or a fatty liver found at post-mortem examination.

The condition produced by the combination of disease and malnutrition may be called " secondary protein malnutrition " (Trowell, 1944). No hard and fast line can be drawn between it and infantile kwashiorkor complicated by an infection ; in both cases the response to the added disease depends on the underlying nutritional state, and the clinical picture is confused.

Probable descriptions of the acute phase in adults

In compiling the following list the same difficulty of selection arose that was met in kwashiorkor in children ; the reports were very often lacking in some important particular which was needed to confirm the diagnosis.

It will be seen that nearly all the reports have come from Africa :

Africa	*Author*	*Year*
Belgian Congo	Dumont	1934
	Cochaux	1937
	Trolli	1938
	Van Daele	1938
	Pieraerts	1942
	Doucet	1946
	Jacques	1947
	Mouchet	1950–51
	Demaeyer	1952 *Proc.*
Eritrea	Ferro-Luzzi	1950
French Equatorial Africa	Georgelin	1920
French West Africa	Jamot	1918, 1920
	Robert, Long, Feyte and Dareys	1933
Kenya	Nicholls	1933
	Gillan	1934–35
South Africa	Grieve	1953
Tanganyika	Stubbs	1920
	McKenzie	1940–41
Uganda	McConnell	1918
	Trowell	1944
	Brown and Trowell	1944
	Trowell and Muwazi	1945–46
	Davies	1948a
	Holmes and Trowell	1948
West Africa	de Castro	1918
Elsewhere		
Haiti	Mann, Helm and Brown	1920
	Mann	1924
	Wickersham	1929
India	Aykroyd and Gopalan	1943
	Hare	1947
	Passmore	1947–48
Indo-China	Thiroux	1920
	Normet	1926, 1928, 1937a, b
	Bablet and Normet	1937
	van Steenis [1]	1950

THE CLINICAL PICTURE, PATHOLOGICAL FINDINGS, DIFFERENTIAL DIAGNOSIS AND TREATMENT OF THE ACUTE PHASE IN ADULTS

1. Age, sex and history

The majority of cases have been young adults, and no reports have mentioned a particularly high incidence in elderly persons. The apparent frequency of occurrence in the younger age groups may have been due to the number of young immigrant labourers observed.

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[1] The man described had been at sea for long periods, in the North and South Atlantic.

It is impossible to say if the disease occurs more commonly in men than in women; most immigrant labourers are men. The disease was said by Doucet (1946) to be commoner in rural districts amongst women, especially among neglected wives living in poverty (see also Trolli, 1938). It sometimes attacks women during pregnancy and during lactation (Doucet, 1946; Demaeyer, 1952 *Proc.*), presumably because their protein requirements are then abnormally high.

The diet in the period preceding the illness has almost always been largely carbohydrate with little protein or fat, and has always been very plain and monotonous. The illness has been most common in times of food shortage (Normet, 1926, 1928, 1937 a, b; Cochaux, 1937; Brown and Trowell, 1944; Trowell and Muwazi, 1945–46; van Steenis, 1950). Some of the patients described had recently undertaken long marches, or some other strenuous physical exertion (de Castro, 1918; Stubbs, 1920; Trowell and Muwazi, 1945–46).

Season appears to have no effect on incidence except in so far as it influences the availability of food.

2. The signs of the acute condition

General appearance. The patients are thin; they lack subcutaneous fat, and although they may be oedematous there is always severe reduction in weight. The muscles are extremely wasted but the wasting may be concealed by the oedema and only becomes obvious when that has disappeared. Contractions of all the muscles can be elicited easily by direct percussion.

The patients are very weak; even if they have no oedema of the legs they are either just able to move very slowly, shuffling along on a broad base (Fig. 28 (*a*)), or are completely confined to bed. The appetite is always reduced and fastidious, and in the terminal stages there is great anorexia, or a positive repugnance to all food. The mental state is one of profound depression and apathy. If they are confined to bed the patients ask only to be left alone, completely unattended, even if the bed is soiled. They finally sink into stupor. Sudden and unexpected death has been recorded occasionally (Mann, Helm and Brown, 1920).

Oedema. Oedema is usual, but is very variable in amount. It may be confined largely to the legs of those who are still walking, and in general affects most the dependent parts, but it makes the face puffy at an early stage. It tends to shift with varying postures of the body. In a few advanced cases there is severe anasarca, and a resemblance to acute nephritis with effusions in the serous sacs; severe oedema of the male genital organs is common.

The patients without oedema appear to fall into two classes; some, such as those adolescents described by Dricot, Beheyt and Charles (1951) are very mildly affected and are not very ill; others, such as those adults described by McKenzie (1940–41) may be dehydrated from severe diarrhoea.

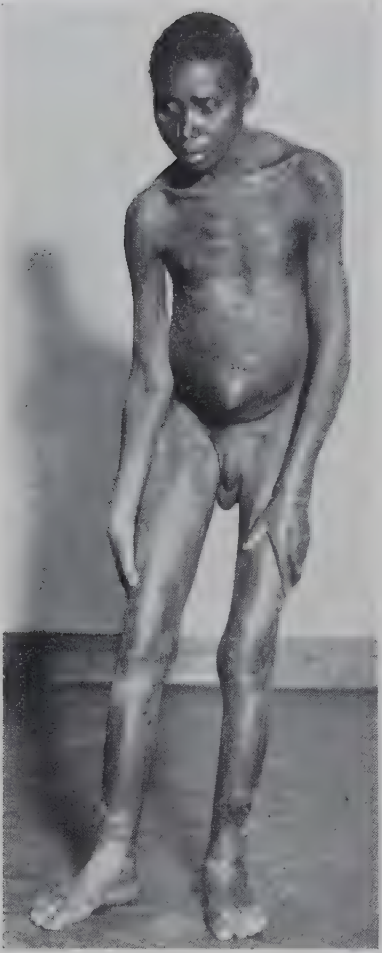
The digestive system. Evidence of some gastro-intestinal dysfunction is always detected if it is looked for carefully. The stools are bulky and loose, their character depending largely on the nature of the food. Very often they are foul-smelling and contain many particles of food which can be recognized even with the naked eye (Mann, 1924; Gillan, 1934–35; McKenzie, 1940–41; Brown and Trowell, 1944; Trowell and Muwazi, 1945–46). If cooked bananas (plantains) are eaten the stools may be soft, but on other diets there may be frank watery diarrhoea.

Fat is not well tolerated and milk is often refused (Normet, 1926). Perhaps because the fat intake is small steatorrhoea is seldom a prominent feature, although it may occur in patients who are re-fed with milk.

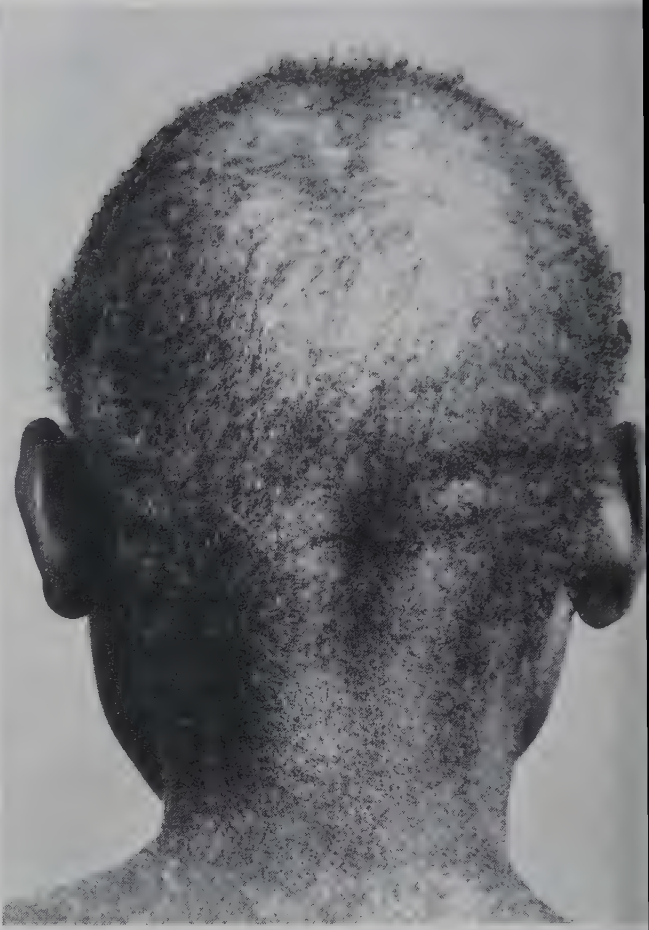
The abdomen usually appears full and may be distended. The patients complain of loud borborygmi, and of sensations of distention and colicky movements which decrease the desire to take food. They have several actions of the bowels just before daybreak and few more throughout the rest of the day. They seldom complain of the frequency of the bowel actions, and are more inclined to demand purgatives which they hope will relieve the abdominal symptoms; the purgatives may, however, produce severe and intractable diarrhoea. There is seldom any vomiting.

The bowel condition is frequently complicated by flagellate infections (Trowell and Muwazi, 1945–46) and in tropical countries both bacillary dysentery and amoebiasis are common.

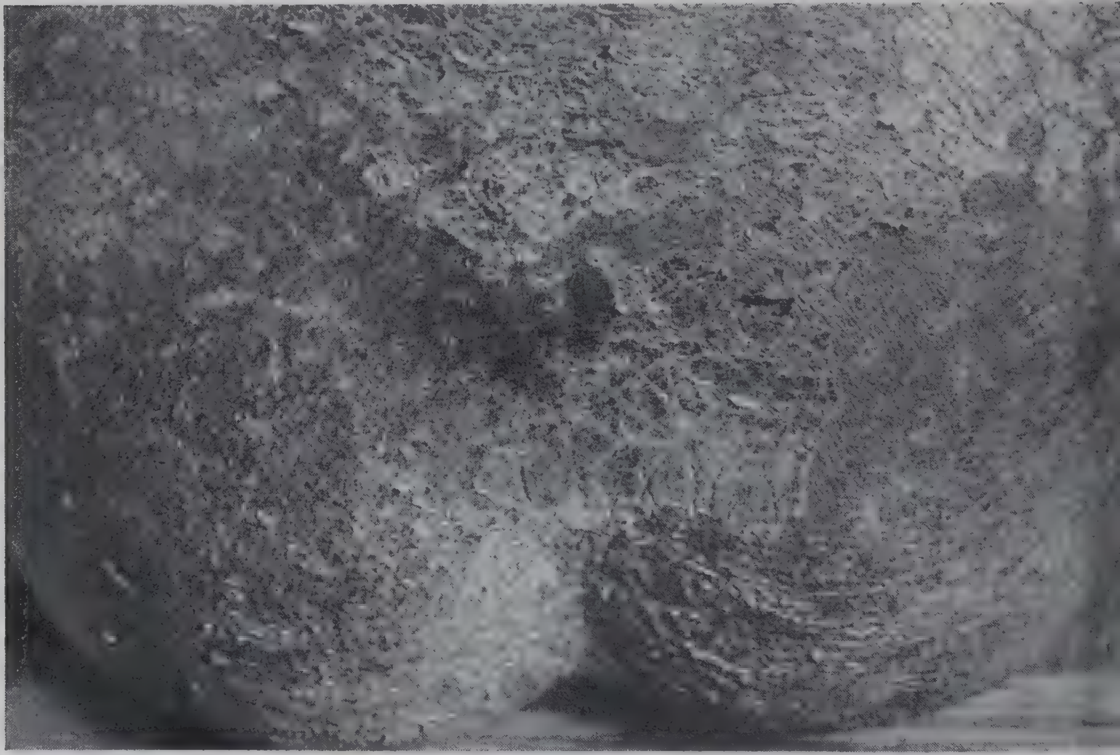
Other evidence of acute and chronic disease of the alimentary



(*a*)



(*b*)



(*c*)

tract can usually be found. The tongue may be red, especially at the edges; its surface may be granular but more frequently is smooth and atrophic. Radiological examination of the gastro-intestinal tract reveals much distension of the colon. A barium-water suspension shows a large amount of segmentation in the small intestine; at one time this "deficiency bowel pattern" (Brown and Trowell, 1944; Golden, 1945) was considered to be evidence of a deficiency of the vitamin B complex, but now it is thought more likely to reflect difficulty in fat digestion.

Kidney function. A faint trace of albumen is often found in the urine; cells and casts are uncommon, but urinary infections by coliform organisms may occur. There are no other signs of renal involvement.

Changes in the hair. The hair usually shows some change but of lesser degree than in children suffering from kwashiorkor. It is almost always soft; it loses most of its curliness and toughness, and its sheen. Black hair may be slightly or moderately dyspigmented. The change in colour affects first the fine lanugo hair, and may be most obvious on the forehead, but can also be seen on the limbs and trunk. If it becomes severe it can be seen in the scalp hairs which may remain jet-black at the roots but be altered at their tips. The dyspigmentation is increased by exposure to sun or air. The eyelashes, eyebrows, moustache and beard and the supra-pubic hair are very resistant to the change of colour. The axillary hair may be misleading as it is sometimes light in colour in men who are apparently well fed. A certain amount of scalp hair may actually be lost, especially from that part of the scalp which is usually in contact with the pillow (Fig. 28 (*b*)).

Changes in the skin. In cases which have marked alterations in the colour of the hair there may also be some loss of pigment in the skin, but it is only in extremely dark skins that any alteration is easily seen. Very often there is no detectable change in the skin colour.

FIG. 28.—Protein malnutrition in an adult.

(*a*) The general appearance. Note the apathetic expression, the weakly held posture, and the oedema of the legs.

(*b*) The head of the same man, showing the altered texture and colour of the hair, and the loss of hair from the back of head.

(*c*) The buttocks, showing dry, unhealthy desquamating skin.

This man was admitted to Mulago Hospital under Dr. P. W. Hutton.

Some dryness and roughness of the skin is very common, and crackling and fine flaking is often to be found, not only over the tibiae, but over all parts exposed to minor trauma. Occasionally " crackled skin " covers large areas of the body (Fig. 28 (*c*)). If it is severe it may desquamate in large superficial flakes during refeeding and convalescence and disclose skin which is more healthy. It may even show a tendency to accumulate an increase of pigment and may then simulate the true " enamel-paint dermatosis " of infantile kwashiorkor. Very occasionally a condition closely resembling that dermatosis occurs as a terminal event shortly before death. It affects sites of pressure and irritation, but is not especially common in the inguinal region, and is not seen over the parts such as the face, hands and feet which are exposed to sunlight. The dermatosis begins as a few small reddish areas which rapidly darken and turn purple and shiny and may become " enamel-paint " plaques. The evolution is slower than in infants, but eventually the plaques peel somewhat superficially, revealing a pale base. Brown and Trowell (1944) observed the typical kwashiorkor dermatosis in an African adolescent and also in Polish women refugees.

Angular stomatitis and other signs of riboflavin deficiency may be found in some adults, but are uncommon.

Neurological and mental changes. No definite changes have been reported in the nervous system of adults suffering from the disease, but tendon reflexes may be reduced and are sometimes absent. There are apparently no sensory changes, but some patients complain of paraesthesiae in the limbs. Neither the peripheral neuritis of beri-beri nor the mania of pellagra have been observed.

The mental apathy, slowness and feebleness of movement have already been mentioned. All sexual desire is lost very early in the disease.

Possible signs of endocrine dysfunction. It has been noticed at Kampala that in most cases of protein malnutrition in adults the hair on the body is very scanty; the supra-pubic hair may be particularly so and have a horizontal upper level in men. Men often have rather thin and high-pitched voices which sound almost feminine, and sometimes slight degrees of gynaecomastia. The exact significance of these observations is not certain as many men who appear to be well fed have a bodily habitat suggesting intersexuality.

Changes in the blood. Some degree of anaemia is present in all adults, but is seldom severe unless an intercurrent infection by a blood-destroying tropical parasite is also present. The anaemia, even when mild, shows the same characteristics as that seen in cases of infantile kwashiorkor ; the colour index is usually within the normal range and the red cells may be normocytic in terms of mean corpuscular volume, but macrocytosis tends to occur as the anaemia becomes more severe, and in terms of the Price-Jones curve can be found relatively early.

If there is a hookworm infection, and especially if it is severe enough to dominate the clinical picture and cause depletion of iron, the colour index, the mean corpuscular volume and mean corpuscular haemoglobin concentration tend to drop below the normal range of values. Markedly microcytic anaemia is, however, uncommon, although hypochromia may become severe ; under iron therapy there is then a brisk reticulocyte response and a very rapid, but temporary, rise of the mean corpuscular volume (Lehmann, 1949). The bone marrow in most uncomplicated cases shows only normoblastic or macronormoblastic changes (Trowell, 1951b) ; if iron-deficiency is also present the appearance of hypochromic erythropoiesis may predominate. It is doubtful whether any characteristic changes in the leucocytes or platelets have been fully established ; at Kampala, neutropenia and thrombocytopenia are common and the leucocyte response to infection is often poor.

The cardiovascular system. The cardiovascular system has been very inadequately examined in adults ; most observers have reported that there were no signs of congestive failure, and have then dismissed the matter. Some slowness of the pulse was noticed by de Castro (1918) and Mann (1924), but this has not been observed or commented on by any other investigators and has been noted but seldom at Kampala, where a normal cardiac rate, or even some tachycardia, is usual. The blood-pressure, both systolic and diastolic, is always low. The myocardial sounds are feeble ; systolic murmurs may occur if anaemia or fever are severe. Cardiac enlargement has not been reported in uncomplicated cases. There has been no study of the radiological appearances or of the electrocardiagram.

3. The pathological anatomy

An account of the early investigations of the pathological anatomy has been given already (p. 122). The studies by Normet of adults in Indo-China were exceptionally thorough. There were references by McKenzie (1940–41) and Passmore (1947–48) to the morbid histology in adults and some notes were given by Brown and Trowell (1944), Trowell and Muwazi (1945–46), and Holmes and Trowell (1948), but there have been no comprehensive studies, and when one of us (J. N. P. D., 1948a) surveyed the field it was largely in an endeavour to link together the successive phases in weanling, childhood and adult life. Most of the studies in adults were made when a large number of cases attracted attention, as when immigrant labourers marched long distances into Uganda to seek work, fell ill and died. Nowadays almost all the labourers come by motor transport and death in the acute phase has become infrequent in Kampala. Improvements in therapy have also resulted in a reduction in the number of deaths in recent years at Kampala, and most of the deaths occur when some intractable infection such as tuberculosis complicates the picture. It is usually only cases with irreversible fibrosis which come to post-mortem, and unless hepatic biopsy is performed and the pancreatic enzymes are estimated many features of the acute phase are missed.

Gross appearance at post-mortem examination. At the post-mortem examination of adults dying in the acute phase at Kampala the macroscopic appearances conform with the clinical findings. The corpse never presents the extreme wasting, the hollow cheeks and the scaphoid abdomen of starvation and hunger oedema ; more often there is a bloated appearance and much oedema and ascites, especially if it has been impossible to give any effective treatment. The external changes in the skin, scalp and hair are usually slight and have already been described. Subcutaneous fat is very scanty and the muscles are wasted. The intestinal walls are usually extremely thin and diaphanous but are only slightly distended with gas. Pallor of the various organs, caused by anaemia, is very variable, and is seldom severe unless an infection is also present. The liver is usually ochre-coloured, sometimes stone-coloured. The cut section often appears fatty, but has a firm texture and clear lobular markings ; sometimes a fine cirrhosis may be suggested to the naked eye. The pancreas is small, atrophied and usually firm and fibrosed. The parotids are often enlarged and firm, and the lachrymals seem to be enlarged if the upper eyelid is everted. The testes may be small, soft and atrophic. The general appearance is not that of a person who had previously an excellent physique, and has recently become wasted, but is that of a stunted person who has recently become oedematous and thin.

Histopathology of the disease. Many organs show a mixture of acute cellular degeneration and chronic irreversible fibrosis; the degeneration varies greatly in degree and if it is slight only the fibrosis may be detected. The amount of sclerosis is also very variable, but is always more severe in adults than in children, and all stages can be detected, up to the frank hepatic cirrhosis and pancreatic sclerosis (Robert, Long, Feyte and Dareys, 1933) which dominate the later, or malignant, stages of the disease. The acute changes in the pancreas, liver and other organs of adults are usually of the same nature as those seen in kwashiorkor in weanlings, although the greatest atrophy is frequently seen in the small intestine. In adults who have suffered a moderate deficiency of protein for a long period of time (and this is the largest group) there is often very little or no excess of fat in the liver, but a great deal of fibrous tissue, and there may be a considerable degree of fibrosis of the pancreas. Atrophy of the acinar cells of the pancreas is always the most constant lesion in untreated cases, although its degree may vary because it seems to yield to treatment. Some amount of atrophic change is present, irrespective of the presence or absence of fat in the liver. Many other organs show changes, but it is difficult to say how far the changes are due to protein deficiency. For this reason, only those organs which appear to be affected in adults both frequently and in a specific manner will be described here.

The pancreas. The major ducts show no changes save that there may be a small amount of retained secretion. The acinar cells show a varying degree of atrophy and degranulation depending partly on the length and severity of the episode of protein malnutrition, and partly on whether the case has received any treatment since admission to hospital, especially by milk and high protein diets. In severe cases there is complete degranulation, the acinar cells being reduced to rims of cytoplasm around rather pycnotic nuclei, but in other cases the acinar cells may be more normal in appearance. There is often considerable variation from one lobule to another, some lobules being almost normal but lying cheek by jowl with others showing marked atrophy. Sometimes there is considerable oedema of the pancreas. Cellular infiltrations—collections of lymphocytes, plasma cells, and even polymorphonuclear leucocytes—may be present. The degree of cellular infiltration seems to bear some relationship to the diarrhoea, being more marked when that has been severe. The cellular infiltration is rarely, if ever, so great that the lesion could be mistaken for a pancreatitis, the picture being dominated by atrophy and fibrosis. The fibrosis is often well marked, with the lobular boundaries well demarcated by thick bands of fibrous tissue spreading outwards from the main ducts and with finer strands penetrating inwards and extending round the tubules and acini. In other cases the fibrosis is less evident, and is irregular and patchy in distribution. In almost all cases more fibrosis is present than could be accounted for by mere condensation of the tissues following atrophy of the acinar cells.

The islets of Langerhans appear to be unaltered.

The liver. A variety of changes may be present. The commonest is an excess of fat in the peripheral cells of the lobules; in severe cases the central cells may also be involved, but the change is seldom as severe as that seen in kwashiorkor in infancy. Under treatment the fat is removed first from the central cells, and only later does it disappear from those at the periphery of the lobule. In infected cases and in those with " secondary protein malnutrition " the distribution of the fat is irregular within the lobule and varies much from one lobule to another.

In certain cases of acute protein malnutrition in adults, no stainable fat can be seen in the liver cells, even in tissue obtained by needle puncture biopsy; the cells are, however, swollen and very finely vacuolated. Other cases may show small liver cells, and dilated sinusoids containing a small amount of protein exudate in the spaces of Disse. In the cases seen in Uganda there has never been any evidence of haemochromatosis or of the " cytosiderosis " of Gillman and Gillman (1948b, 1951), but variable amounts of perinuclear brown pigment, which does not give the Prussian blue reaction, have been found. Malarial pigment is seen much less frequently in adults than in children, but a fair amount occurs in African immigrant labourers who have come from areas where there is little malaria to work in the hyperendemic areas of Uganda.

The principal point of difference between the histological appearances in children and adults lies in the far greater amount of hepatic fibrosis seen in the adults. The fibrosis consists chiefly of a great exaggeration of the stellate fibrosis seen in children, and, in the opinion of the writers, presents certain points of distinction from that seen in a fine cirrhosis of the Laennec type as encountered in temperate regions. In adults in the Tropics fine strands of fibrous tissue extend outwards from the portal tracts to delimit the lobules, and small extensions run from the periphery down the sinusoids. There is a very marked cellular infiltration in the portal triads and along the interlobular fibrous bands, chiefly of mononuclear cells, macrophages, lymphocytes and plasma cells; sometimes neutrophilic and eosinophilic polymorphonuclear cells are seen in considerable numbers. The fibrous bands may join portal tract to portal tract, forming an annular monolobular type of cirrhosis, reminiscent of a biliary cirrhosis, save that there is no evidence of any obstruction, dilatation or inflammation of the bile ducts. Bile-duct proliferation is not present during the early stages.

It is probable that in the early stages of an acute episode in an adult there is usually a fair amount of fat in the liver, but there may be no more fibrosis than that frequently seen in ordinary adult Africans. Later on, if attacks recur and the diet remains unsatisfactory, fibrosis may increase, while at the same time the fat may diminish. The evidence available to the writers is far too fragmentary to lend any weight to the statement that the fatty infiltration in untreated adults *leads* to the increase of fibrous tissue, for their experience has only lain among cases treated for a short time in hospital and examined repeatedly by needle puncture biopsy. The study of the natural sequence of events in individual untreated cases has not been possible. Slow progressive fibrosis over a period of several years appears to be the usual course, and strands of fibrous tissue often seem to cut off small groups of cells at the periphery of the lobules. As the fibrosis increases more severe signs of obstruction of the finer biliary ducts can be recognized; there is dilatation and plugging of the caniculi, some proliferation of the bile ducts and increased pigmentation in the liver cells. At the same time nodules of hyperplasia appear, but usually remain very small in size, being barely visible to the naked eye. Destruction and regeneration probably proceed simultaneously. Areas of necrosis have not been detected, but the death of many individual cells is probable. The exact method of evolution of the fine cirrhosis which eventually dominates the picture is uncertain.

The small intestine. Adults usually show more severe changes in the intestines than do children with kwashiorkor. The gross atrophy of the intestinal wall was emphasized by McKenzie (1940–41) in Tanganyika and by Passmore (1947–48), in India; similar changes were produced in monkeys by Radhakrishna Rao (1942), who gave a diet consisting largely of milled rice. The intestines are often as thin as paper and are almost transparent. All coats are affected in severe cases; the mucous membrane is shrunken, the villi are atrophied and the muscularis mucosae is barely visible. The external muscle coats may be grossly atrophied and the lymphoid tissue may be very scanty and inactive in appearance. No special studies have been made of the nerve plexuses. The early degranulation and atrophy of the enzyme-secreting cells and Paneth cells is much more difficult to establish in adults than in children.

The parotid glands. These glands have been fully studied by Gillman, Gilbert and Gillman (1947) in all phases of chronic malnutrition in South Africa: they have not been examined so completely at Kampala. Little is known about the sequence of events, but in the acute phase there would appear to be an atrophy of the secreting cells. An increased amount of fat is often present, and there may be some excess of fibrous tissue. Infiltrations with chronic inflammatory cells may be marked. In the submaxillary glands there are atrophic changes which affect the secretory cells rather than those responsible for the formation of mucus, so that typical crescents are rare.

4. Biochemical changes

There have been very few studies of the biochemical changes of the acute phase in adults, apart from reports on the serum proteins. Trowell and Muwazi (1945–46) found a mean serum albumen of 2·09 g./100 ml. and a mean serum globulin of 4·61 g./100 ml.; similar results were found in another series of fourteen cases by Holmes and Trowell (1948) and in one case by van Steenis (1950). The low blood urea, and the low daily excretion of urea in the urine were stressed by Normet (1926). In one adult case recorded by van Steenis (1950) a reduction in the activity of the pancreatic enzymes was found. Recent work in Kampala (Thompson, to be published) showed in five cases that there were reductions of trypsin, lipase and amylase, and that diets rich in protein brought about some measure of recovery. Trowell and Muwazi (1945–46) and van Steenis (1950) reported hypochlorhydria or achlorhydria, even after histamine.

Holmes and Trowell (1948) demonstrated a failure of the liver cells to store glycogen when presented with glucose by intravenous injection. In one case the fasting blood sugar was very low, being only 29·0 mg. 100 ml.; the patient, who was comatose, revived temporarily on being given intravenous glucose but died within a few hours. At autopsy a fatty liver and an early fibrosis of the pancreas were found. There have been no estimations of the blood enzymes in adults.

The biochemical changes found in some adolescent boys by Dricot, Beheyt and Charles (1951) are described on page 178.

5. Complications

The majority of the adult cases of kwashiorkor seen at Kampala have some infection, but it is doubtful if, apart from flagellates, infections are any commoner than among routine admissions to medical wards (Trowell and Muwazi, 1945-46).

Infections of the skin, and a terminal pneumonia, are very frequently seen. The relationship of protein malnutrition in adults to infection is a relatively unexplored field; experience at Kampala has suggested that, if any case is not responding to large amounts of milk protein, which is supplementing a balanced and ample diet, there is present either some untreated infection such as tuberculosis or a serious condition of another kind, such as chronic nephritis or hepatic cirrhosis. Minor infections, such as a few helminths in the intestines or a few malarial parasites in the blood, seldom appear to delay recovery. Treatment of the infection unaccompanied by dietetic treatment is often disappointing, although heavy infections certainly require treatment. If adults thought to be suffering from an acute episode of protein malnutrition come to post-mortem, more sclerosis of the pancreas and liver is usually found than was expected in life, and this may explain the failure of certain cases to respond to treatment (Holmes and Trowell, 1948; cases 1, 5, 10).

6. The course and mortality

An acute episode of protein malnutrition in adults is always a serious disorder, and untreated cases have a high mortality. Even with treatment the death-rate is high; anorexia limits the intake of food and the failure of digestion prevents the protein in the diet from exerting its full beneficial effect. Similar statements concerning the course, mortality and difficulty of treatment have been made by many observers (Jamot, 1918; McConnell, 1918; Stubbs, 1920; Mann, 1924; Mann, Helm and Brown, 1920; Normet, 1926, 1928; Trolli, 1938; McKenzie, 1940-41; Brown and

Trowell, 1944; Trowell and Muwazi, 1945–46). Most of them reported a death-rate of 10 to 20 per cent, but the rate has certainly been decreased since dried skimmed milk became available. Even ordinary cow's milk may benefit many cases, and at Kampala high mortality rates were only reported when it was unobtainable (Trowell and Muwazi, 1945–46).

7. The differential diagnosis

As distinctive changes are seldom seen to any marked degree in the hair and skin, the principal diagnostic criteria are loss of weight, oedema, and the presence of undigested food in loose stools. In addition, the diagnosis is strengthened if it can be ascertained that the previous diet has been very low in protein and inadequate in its total calories, especially in relation to the amount of physical labour undertaken. A good response to high protein diets, particularly those containing much skimmed milk, is further confirmation, especially if there is intolerance of whole milk and little progress on a full balanced diet.

Differentiation of the oedema from that of congestive cardiac failure and beri-beri is usually easy. Since slight albuminuria may occur, differentiation from chronic nephritis is important but is possible by the further examination of the urine and by measurement of the blood-pressure. The oedema associated with anaemia, and the hunger oedema due to caloric deficiency may both cause difficulties. Misgivings are decreased if it is recognized that many cases may have one or both of these conditions as well as protein malnutrition. Anaemia is perhaps more likely than caloric deficiency to produce a clinical picture resembling that of protein malnutrition, especially if the anaemia is caused by a heavy and prolonged infection or infestation which depletes the body of protein or upsets its metabolism. This is especially true of hookworm anaemia among poorly-fed persons, and in the present state of our knowledge complete separation of hookworm disease and protein malnutrition is somewhat arbitrary. Hookworm disease, accompanied by moderate or severe anaemia, is very seldom found in Kampala in people who are well fed; such people may carry over a thousand *Necator americanus* worms and have little or no reduction of haemoglobin, and no oedema. Experience in Uganda suggests that in any one complex adult case it is more common to overlook the element of protein malnutrition than the cause of the anaemia.

A man may be admitted with the diagnosis of hookworm anaemia, and iron and a mixed diet may be given. He dies, and at autopsy very few hookworms are found despite very careful search, but all the features of protein malnutrition may be detected. At the other end of the series of combinations of the two conditions there are cases in which, erroneously, protein malnutrition was suspected to be dominant until it was realized that no progress was being made on a diet of skimmed milk, a suitable carbohydrate and oral iron. In such a case, an anthelmintic may produce 1,000 to 2,000 worms, and an improvement of all aspects of the patient's condition (Lehmann, 1949). These observations apply, but to a less extent, to other infections, including all those by helminths, to bilharzia, malaria, trypanosomiasis, kala-azar, amoebiasis, tuberculosis and leprosy. Any of the infections or infestations may complicate, or perhaps lead to, an acute episode of protein malnutrition in adults, but none of them appears to produce as much protein depletion as the blood-sucking hookworm.

The differentiation from hunger oedema (p. 117) is made chiefly on the history of the preceding diet. In protein malnutrition in adults there is a striking absence of hunger, and the oedema is usually gross ; the serum albumen is severely reduced, there is undigested food in the stools and the response to an apparently adequate mixed diet is poor. At post-mortem the pancreatic atrophy and the fatty liver make the distinction certain. Other diseases with chronic diarrhoea—chronic steatorrhoea, sprue, intestinal tuberculosis, and amoebiasis—must be differentiated by the usual methods of investigation.

8. Treatment

In general, the most satisfactory treatment is similar to that of acute kwashiorkor in children, but adults tolerate whole cow's milk better than do children. Other sources of protein, such as beans and meat, can be added at an earlier stage than would be safe in infants. Because full milk may be tolerated, many who feel that milk should be given to any sick person may miss the distinctive features which point to a diagnosis of protein malnutrition. Advanced cases, however, tolerate milk and fat poorly (Normet, 1926, 1928) and should be treated along the lines employed in acute kwashiorkor in young children. Skimmed milk protein is of great value. It is important to give, if possible, large amounts ; 100 to

200 g. *of protein* should be given each day in a diet providing at least 3000 calories. At first this may be difficult because of the anorexia and because increases of the diet may provoke diarrhoea.

All bacterial and protozoal infections require treatment as soon as they are detected, but helminthic infections are best left untreated, unless they are especially heavy, because therapy is apt to cause diarrhoea, or serious damage to the liver.

Because of the difficulty of establishing intensive treatment, signs of recovery are slow to appear, and a dramatic reduction of the oedema, as in the infantile cases, is seldom seen. Considerable patience and skill is required in the early stages of treatment. If cases are really not responding, despite a high protein diet which also provides adequate calories, two questions should be asked. Has any infection such as tuberculosis been missed, and how far have irreversible sclerotic changes occurred (Holmes and Trowell, 1948)?

Even with the best treatment convalescence is always slow and protracted and it is many months before recovery can be deemed to be complete.

Mild protein malnutrition in adults

It is probable that a large number of adults in tropical countries live on diets in which the protein/calorie ratio is from 1·5 to 2·5 g. protein/100 calories. The British Medical Association Committee on Nutrition (1950) recommended 3 g. protein/100 calories in adults. A survey of Kampala workers in September 1951 (East African Statistical Department, 1951) indicated a mean daily intake of 44 g. protein and 2015 calories, or 2·2 g. protein/100 calories; about one third of the protein was taken as beans, which are a seasonal crop and not always obtainable in Uganda. The inadequate intake of protein, by itself, seldom causes any clear signs of illness, but many African labourers are rather underweight, have poorly developed muscles, fatigue easily, and have hair which is slightly soft and has a slightly brownish sheen; if sudden traumatic death occurs, some fatty infiltration of the liver is often found (Gillman and Gillman, 1946), and the pancreas shows mild atrophic changes. Other abnormalities which may be detected during life are a mild anaemia, often normocytic or slightly macrocytic (p. 102), or abnormal serum proteins (p. 163); such findings may reflect acute (reversible) or chronic (irreversible) changes.

If these cases of " mild protein malnutrition " suffer a period of reduced food intake, possibly combined with an infection, protein deficiency becomes acute and certain aspects of the kwashiorkor pattern may emerge in sharp outline. For instance, oedema may appear in typhoid fever, or around the stitches of a surgical wound, or become suddenly severe in cardiac or renal failure. Similarly, anaemia may become very marked in helminthic infections or tuberculosis.

Discussion

Is the picture—clinical, biochemical, pathological and therapeutic—so clear that it is justifiable to speak of a distinct disease-process in adults ? If so, is the picture so like that seen in infants that it can be given, at least provisionally, the label of kwashiorkor ?

Adults, even Africans, very seldom display two of the most distinctive features seen in children—the " enamel-paint dermatosis " and definite dyspigmentation of the hair. This fact, more than anything else, led some observers at one time to consider that the term kwashiorkor was unsuitable for the adult cases (Trowell, 1944). Neither the dermatosis nor the dyspigmentation is, however, now regarded as an essential criterion of kwashiorkor as seen in infancy, so that their absence ceases to be a serious objection.

Finally, it may be said that protein malnutrition in adults may occur when a diet, already low in protein, is rendered less adequate by any of a number of causes—extra physical exertion, fever, pregnancy, and so on. These factors assume greater importance if the liver and the pancreas are already damaged ; the full benefit cannot be obtained from the food that is taken and the effects of the extra strain are increased. If the liver becomes fatty there may be, as in any liver disorder, anorexia which further reduces the consumption of food. The sequence of events is not that which produces hunger oedema. The adult who is pushed into protein malnutrition has for a long time been living on the brink of it : hunger oedema, on the other hand, appears at the end of a long period of generalized food reduction. In some particularly unhappy circumstances, the two conditions may be combined ; India seems to offer many examples. In the majority of cases seen in Kampala, and, it seems, in many other places, protein malnutrition—shall we say " adult kwashiorkor " ?—appears to dominate, or to reign alone.

PART V

IMPLICATIONS OF KWASHIORKOR IN CHILDREN AND OF PROTEIN MALNUTRITION IN ADULTS

It would be unwise to invoke a deficiency of protein, or of any other specific dietary factor, to explain all the differences found between Europeans and the peoples who inhabit the Tropics, but it may be profitable to review some medical aspects of the African scene and to consider how likely or unlikely it is that diet is responsible. The experience of the writers has been confined largely to Africa, and the concentration on Africa is deliberate. It seems possible, however, that if an attempt is made to cover one continent, itself so vast that it contains a great diversity of ethnic types, of cultures, and of climates, observers in other continents will be stimulated to do the same.

There are some facts that can be stated without much fear of dispute. A large part of the population of Africa, and undoubtedly of many other continents, are living today on inadequate diets and much of the inadequacy must be of protein. In those countries, the make-up of the population is not that of the well-fed countries of Europe or of the United States ; the pattern of disease is different, and the ability to perform hard physical work is different. The implications of an inferior physique are not fully understood, but there is a general tendency in modern medicine to find more and more connection between physical and mental conditions. It is not impossible that the reluctance or the inability to perform sustained mental work which is a common finding among culturally retarded peoples may be related to the dietary background. An excellent discussion of this subject, and of much else that is relevant, will be found in the monograph by Carothers (1953).

1. Changes in the liver

Although there is at present little known connection between the fatty livers so often found in infancy and stellate fibrosis and cirrhosis in adults, there is no doubt of the great frequency with which marked signs of disease can be found in the livers of Africans. Gillman and Gillman (1948b) found such signs in 174 out of 261 livers of persons who had died suddenly. Only seven of the livers were considered to be fatty, but Vint (1930–31) found fatty infiltration in 72 out of 100 consecutive post-mortems in Nairobi. Some of the deaths in this series, however, were from infections which probably led to the increase of fat, especially in the central portions of the lobule.

It seems certain that in many Africans as age advances more and more stellate fibrosis occurs in the portal tracts and encircles the edge of the lobules. The exact stage at which the term cirrhosis should be applied to this progressive pathological process is a matter of opinion; most pathologists would apply the term cirrhosis only to those cases which showed gross disturbance of the lobular pattern by fibrous tissue and nodules of hyperplasia. At Kampala, any increase of fibrous tissue arising around the portal triads is regarded as abnormal. Like other fibrous tissue it tends to remain and to contract, and in contracting it constricts the nutrient vessels. The changes constitute the stellate fibrosis which eventually pervades the whole liver. Complete compensation, or even restoration of the normal liver pattern, might be possible if a diet rich in protein and the vitamin B complex was given, but that can have been done very seldom in tropical Africa. It is probable that in the livers regeneration proceeds slowly all the time, as shown by the frequency of binucleate hepatic cells (J. Gillman, 1940; Bergeret and Roulet, 1947; Roulet, 1951).

The discovery of cirrhosis which was unsuspected during life is common at post-mortems on Africans. Reliable evidence of stellate fibrosis and cirrhosis can only be obtained during life by needle biopsy, or at post-mortem examination, and even then special techniques have to be used if the full extent of the fibrosis is to be determined. Although he did not, apparently, use such techniques, Vint (1930–31) found an abnormal degree of fibrosis in 63 out of 100 consecutive examinations.

It might be argued that the finding of histological appearances which are different from those considered normal in Europe or in America does not of itself constitute certain evidence of disease, but there seems to be no doubt that the frequency of abnormalities in African livers is matched by the high incidence of hepatic troubles. Trowell (1932–33) noticed that jaundice developed in about a quarter of the cases of lobar pneumonia in Nairobi and thought that the highest mortality was amongst those who were malnourished, anaemic, and had grossly enlarged spleens. Gelfand (1947) discussed in detail the frequency of the occurrence of jaundice in Africans, not only in pneumonia but in typhoid, tuberculosis and meningitis, infections which very rarely cause jaundice in Europeans.

During the period of economic depression from 1936 to 1938 in the United States, Turner, Bent, Holloway, Cuff and Quinland (1943) noticed a high incidence of jaundice in negroes suffering from lobar pneumonia and thought that a lack of protein in the diet might be a predisposing factor. They tested this theory by an experiment in which dogs on a protein-deficient diet were infected with pneumonia. The lungs showed a severe type of pneumonia, the livers showed fatty degeneration and necrosis, and there was a rise in the serum bilirubin. All these phenomena, which are frequently seen in Kampala in African adults suffering from pneumonia, were much less marked in a control group of dogs who had been on a full diet. The tendency to develop jaundice easily is probably related to the frequent occurrence of degenerative and necrotic conditions, after exposure to known (and unknown) hepato-toxic drugs.

The liver is believed to be the principal site of manufacture of the serum proteins and it is a well-known fact that in many liver diseases the level of albumen falls and that of total globulins rises, most of the rise occurring in the γ-fraction. In a group of African college men Holmes, Stanier, Semambo and Jones (1952) found an average of 6·42 g. total protein/100 ml. serum with an albumen/globulin ratio of 0·94, and in the same students after six months' good feeding an average of 7·52 g. total protein and an albumen/globulin ratio of 1·30. The increase in protein was almost entirely in the albumen fraction. Holmes *et al.* did not consider they were in a position to state if the low initial findings reflected a poor nutritional state or a response to infection, but various workers in the Belgian Congo are firmly of the opinion that the abnormalities of the serum proteins commonly found in Africans are the results of nutritional stress affecting especially the liver. There is some evidence that the abnormalities are acquired and not inborn ; the cord bloods of African babies in the Congo were found to have protein fractions which were normal by European and American standards (Symul, 1950 ; van Oye and Charles, 1951a).

Most of the tests of liver function which are in common use depend on the γ-globulin fraction of the serum. van Oye and Charles (1951c) found that 72 out of 600 persons of different ages and both sexes in the Belgian Congo gave positive results in all the seven tests they used. It cannot be said, however, that such a finding is necessarily indicative of a serious state of disease since the γ-globulins are known to increase in infections, especially in malaria (Jager and Nickerson, 1948; Taylor, Mickelsen and Keys, 1949; see also p. 231). Similarly, the level of 1·0 mg. or more bilirubin/100 ml. serum which van Oye and Charles (1951b) found in 30 out of 353 adults cannot be considered to have great pathological importance.

2. Changes in the pancreas

The recognition of the pancreatic changes in kwashiorkor has been comparatively recent and the pancreas has not been studied fully in adults. In 165 unselected autopsies Davies (unpublished results) found fibrosis of the pancreas in 103, and more recent work at Kampala has confirmed that varying degrees of atrophy and sclerosis are frequently to be found.

3. Changes in the blood cells

It is a remarkable fact that although many of the diets eaten by Africans must contain very little animal protein, and therefore very little vitamin B_{12}, there are few reports of anaemias in Africans which respond to treatment with that vitamin. Foy, Kondi and Hargreaves (1952) and Foy and Kondi (1953) described megaloblastic anaemia in Kenya, mostly in pregnant women, which responded to folic acid and sometimes to vitamin B_{12} and refined liver extracts, and to penicillin. Anaemia of this kind has not been commonly found in other parts of Africa. If it has a nutritional origin, its rarity in one place and not in another would not be too surprising, because diets differ greatly in various parts of the continent. The anaemia has been frequently seen in India, especially in pregnancy, and there also occurs in India another anaemia, often macrocytic, which is refractory to treatment by many of the substances which cure pernicious anaemia, but is, nevertheless, considered to be of nutritional origin, an inadequate intake of protein being the possible cause (Passmore, 1947–48, 1948–49). It has also been found in Uganda, usually in association with iron deficiency due to hookworm disease, in a combination which was named "dimorphic anaemia" (Trowell, 1942–43, 1943–44). There seems to be some correlation between the severity of the anaemia and chronic protein malnutrition, liver damage and disturbance of the serum proteins. Woodruff (1951, 1952 *Proc.*) has made an intensive study of this anaemia in Nigeria and has stressed the peculiar dimensions of the red cells : they are broad and thin, and tend to be macrocytic and hypochromic.

4. Endocrine glands and gonads

The association of sex hormone disturbances with liver disease has been known for many years. The literature has been reviewed by Lloyd and Williams (1948), Biskind (1949) and Long and Simmonds (1951). The syndrome in boys and men usually includes feminization, gynaecomastia, testicular atrophy and loss of libido, decrease in axillary, pubic and body hair ; in women, excess of oestrogens may lead to dysmenorrhoea, menorrhagia, a persistent oestrogenic endometrium, uterine subinvolution and cystic mastitis. Many of these manifestations are commonly seen in Africans (Davies, 1949). The hormonal balance is an extremely delicate one, as has been shown by Ferret (1950), but the exact mechanism is imperfectly understood. The changes correspond broadly to those produced by the administration of oestrogens, but it is uncertain as yet if the major factor is the inability of the liver to metabolize or detoxicate oestrogens, or whether there is a perverted conversion of androgens to oestrogens. Further work is needed before it can be said whether or not the damaged liver of the African functions normally in regard to these hormones.

The pituitary gland in adult Africans has been studied exhaustively by T. Gillman (1940, 1942) and Vint (1949) and it is only possible here to summarize briefly their findings. Gillman commented on the high incidence of colloid-containing and vacuolated beta (Crooke) cells, leading to definite cysts (Gillman and Gillman, 1951). The cysts were found in 14 out of 26 cases of chronic malnutrition, and were frequently lined by ciliated epithelium. There was atrophy of the whole pituitary gland, and especially of the pars tuberalis, in many cases. There was sometimes an increase of the basophil cells in the pars posterior, as in Cushing's syndrome in castrated persons. Vint (1949) studied the pituitary gland obtained from 50 fresh autopsies performed in Nairobi and endeavoured to obtain material from cases undergoing sudden accidental death. He performed Rasmussen counts, following strictly the procedure laid down by that investigator, some 10,000 cells being classified and counted in each gland. He concluded that the African men had 8·6 per cent more acidophils and 2·5 per cent less basophils than European men, and pointed out that the figures for the African men were very close to figures obtained from white women. When there was severe liver damage (cirrhosis or hepatic carcinoma) the basophil count was increased. Vint also drew attention to the frequency with which an enlarged thymus gland was found in adult Africans at autopsy.

No comprehensive and systematic study has been made of the suprarenal gland in Africans, although the gland is known to be affected in chronic inanition (McCarrison, 1918–19). Among African adults Gillman and Gillman (1951) often found gross atrophy, with a thin cortex and a relatively thick medulla. The cortical cells showed poor differentiation and a reduction in lipoid, and wide bands of connective tissue separated the cortical trabeculae. The structure and function of the suprarenal glands is of interest not only in connection with upsets of the steroid hormones, in which they may play some part, but also in relation to the action of adrenocorticotrophic hormone (ACTH) and cortisone in normal physiological processes and in a large group of diseases, most of which have an obscure aetiology. Many of the so-called " diseases of stress " (Selye, 1950) are peculiarly rare in Africa among the negro population (Trowell, 1950b). Certain of the diseases are more common among the groups who are becoming better fed and are being subjected to increased and continuous mental strain, especially that imposed by education. All the diseases appear to be as common in American negroes as American whites, so that race is unlikely to be an important factor in aetiology. They are relatively common among Europeans and Indians resident in East Africa, so that climate by itself appears to be an inadequate explanation. It might seem at first sight easy to explain the absence of stress diseases by the supposed tranquillity of African peasant life, but it should be pointed out that the tranquillity is largely a fiction born of European ignorance. The African peasant has anxieties of a special kind—fear of witchcraft, uncertainty of food supplies, perpetual insecurity, poverty, and difficulties in personal affairs. The African must have his share of stress, but may react to it in a way that is different from that of the European—possibly because there are differences in the mechanisms which convert the stress into recognizable somatic disorders. It is likely that there is a hormonal component in the metabolic background of many of the diseases that are rare in parts of Africa. In this group are rheumatoid arthritis, acute rheumatism, thyrotoxicosis, severe hypertension, atheroma, coronary heart disease, angina of effort, ulcerative colitis, insomnia and some forms of anxiety neurosis ; even the infrequency of disseminated lupus erythematosis, atopic dermatitis, eczema, hay-fever and status asthmaticus may be of importance as evidence, since the administration of ACTH is said to influence their course. In all this discussion, and indeed in any consideration of the endocrine pattern in Africans, the lack of any quantitative data makes any final judgement impossible. Almost the only available data are estimations of the excretion of 17-ketosteroids, and they are confusing. Barnicot and Wolffson (1952) found a mean excretion of 17-ketosteroids of 7·97 mg./24 hours in Nigerian Africans, but among Europeans, in Nigeria or England, the mean excretion was 13·71 mg./24 hour. Nothing is known concerning the significance of this marked difference ; evidence that it represents a racial peculiarity might be adduced from the fact that students and laboratory employees in West Africa and West African students resident some years in Britain had equally low levels of excretion.

There has been no recent systematic study of the thyroid gland in Africans, possibly because abnormality is seldom seen at autopsy or at operation. Stein (1938) considered that the follicles of the thyroid were smaller in adult Africans than in Europeans, but he had no satisfactory data on which to base his comparisons. No less an authority than Sir Arthur Keith (Vint, 1949) stated that mild hypothyroidism is almost a racial feature of the African negro. As Gillman and Gillman (1951) remarked, there is much to suggest hypothyroidism in many African adults who have little hair on the outer third of the eyebrow, a harsh dry skin, mental inertia and diminished sexual function, and they observed some atrophy and fibrosis, and large cystic follicles, in thyroid glands obtained at routine autopsies. They advised caution in interpretation as the gland might have altered during a terminal infection. The rarity of cases of hyperthyroidism among Africans is a commonplace among clinicians in Africa and has been discussed by Beyers (1927) and Gillman (1936). Most doctors in tropical Africa have never seen a case in an African, but cases in other races are relatively common. Even more significant is the placidity of so many African women, and the apparent absence of tension and irritability. Simple colloid goitre is very common in certain regions, and is doubtless due largely to a deficient intake of iodine. Cretinism seems to be unknown (Carothers, 1953).

The state of hypothyroidism, if it is that, cannot be ascribed with certainty to a lack of protein in the diet, but it is worth remembering that even mild degrees of undernutrition are commonly associated with a lowering of the basal metabolic rate. The rate was measured in about 100 young adults in the Belgian Congo by Bouckaerts (1948) and Dierckz and Helmons (1950). It was about 5 per cent lower than the normal European value.

With so much abnormal that might affect the sex hormones—the liver, pituitary, suprarenal and thyroid—it is no wonder that the secondary sexual characteristics of many African men are ill-defined. There is little growth of beard or moustache, or of hair on the body, and the suprapubic hair often has a horizontal upper limit. The physique is slender and the sexing of bones, usually an easy matter for the anatomist, may be difficult or impossible. To ascribe such findings to racial characteristics is to deny one of the recurring themes of this study: heredity, food, and environment produce the norms in any community; inherited characteristics never operate by themselves *in vacuo*.

Testicular atrophy is frequently seen at clinical examinations of African adults in Kampala, and is commonest in those who present signs of chronic protein malnutrition, especially those who have cirrhosis. Lack of sexual power is frequently a cause for seeking medical aid, even among young adults. Seminal counts have often proved low in those investigated, but there has been no systematic study of male fertility. The testes have been seldom examined at autopsy and examination by biopsy has not been practised. Gillman and Gillman (1951) have examined the gonads in adult African males and have described much atrophy, with the various stages of spermatogenesis suppressed, possibly involving the tubules in an irregular manner, so that some were spared and others seriously deranged. The interstitial cells were often but little affected.

There has been no systematic study of the prostate or of the seminal vesicles in Africans, but cases of prostatic obstruction due to benign adenomata are uncommon at Kampala.

The presence of gynaecomastia in African adults has attracted some attention. Thus Trowell (1949) thought that 5 per cent of the railway porters in Nairobi showed an abnormal amount of breast tissue. Gillman and Gillman (1951) found the same incidence in their African adult pellagrins. They made some study of the changes and reported that the lactiferous sinuses were enlarged and contained much secretion, and that the tubules were prominent and showed secretory activity ; the gland in many ways resembled the virgin breast, containing much intertubular tissue and some fat.

There is little to note in connection with the hormonal control of carbohydrate metabolism. There is, however, some disturbance of glycogen formation in the liver in acute kwashiorkor in adults (p. 262). Diabetes is uncommon among Africans (Harvey, Titman and Pearson, 1951), as is gross obesity. van Oye and Charles (1952a) considered that Africans in the Belgian Congo had a normal blood-sugar curve.

5. The pattern of disease

(*a*) *Medical conditions.* The concept of a close relationship between undernutrition and response to infection was supported by Cannon (1949), but is not universally accepted.

The infections to which African adults are prone have been the subject of many studies by clinicians and pathologists. The outstanding fact appears to be the unexpectedly large number of deaths in early adult life from ordinary infective disease (Davies, 1947 ; Cullinan, 1945–46). There is agreement that the deaths are seldom due to tropical parasites, but are much more often due to the cosmopolitan infections (p. 281). The presence of much infectious illness among adults is certain ; it is, however, impossible to say if it is commoner or more fatal among Africans who are malnourished.

Tuberculosis holds a special place among the infections which are both unduly common and which display certain peculiar features in Africans. Its frequency is reflected in the autopsy figures which are probably a more accurate indication of the extent and severity of the disease than they are in the case of pneumonia. Haynes (1951) in his recent monograph from Kenya has indicated the difference between the approaches of the epidemiologists and the pathologists. Among the latter Vint (1928–29, 1936–37) and Davies (1947, 1948c) stressed the acuteness of the tuberculous process with little attempt at localization by fibrous tissue. The considerable enlargement of the lymph nodes in many cases suggested that the condition had evolved directly from a primary tuberculous complex. Chronic fibroid phthisis has been rarely seen and evidence of successful limitation of the process has been uncommon. Apical scars or calcification have been rare at autopsy or on the radiological film. Numerous clinicians in Africa have expressed similar views (Matthews, 1935; Wilcocks, 1935; Lyle Cummins, 1939; Gelfand, 1944; Oswald, 1946; Clark, 1951b). Others, however, have considered that chronic phthisis was not uncommon (Wilson, 1927–28; Stones, 1928–29; Burrows, 1935; Davies, 1946; Haynes, 1951). The evidence from tuberculin surveys has shown widespread occurrence of tuberculin sensitivity, but that is of doubtful significance (Edwards, Palmer and Magnus, 1953). Racial factors doubtless have played a part, but most observers conclude that malnutrition is probably a more important factor. Even in European countries where the diet is usually adequate it is generally considered that there is some connection between tuberculosis and undernutrition. The connection may be closer in Africans in whom symptoms reminiscent of an acute attack of kwashiorkor occasionally arise in the course of infection.

Syphilis is very common in many parts of Africa, but the incidence may be somewhat less than that shown by routine serological tests; the tests give positive results because they may depend upon abnormalities of the serum proteins which are not syphilitic in origin.

(*b*) *Surgical conditions.* Tropical ulcer, of which the aetiology has for a long time been a matter of some dispute, seems to be frequent amongst malnourished persons and rare among those who take much animal protein or fish (Forbes Brown, 1930, 1935; Clements, 1934, 1936; O'Brien, 1952). It is virtually absent among well-nourished Africans and Europeans, which makes it more likely that malnutrition, and protein deficiency, may play an important part. Pyomyositis is another disease which is practically limited to those areas of the world and to those social groups in which protein malnutrition is likely to occur.

In Africans, chronic sepsis is more frequently accompanied by oedema and a severe degree of anaemia than in well-fed Europeans. It seems as though the tendency is always latent, and the pathological states appear as soon as the extra strain is added.

All young children have pot-bellies, but the condition is exaggerated, even up to the age of adolescence, in African children (Jelliffe, 1952), and the commonness of a hernia crowning the umbilical region in Uganda may account for its appearance in the carved shape of some of the local musical instruments (Trowell and Wachsmann, 1953). Laxity of the abdominal musculature may be a sign of poor general physique, or a result of taking food of excessive bulk; whatever the cause, inguinal hernia—often direct—is extremely frequent (Van der Elst, 1947; Fain, 1948). The intestines themselves, or their supports, seem to share in the general weakness, to judge from the commonness of intussusception and volvulus, which are amongst the chief abdominal emergencies in African adults (Burkitt, 1952).

(*c*) *Cancer*. It is only in recent years that hospitals, autopsy records and pathological services have become sufficiently established at least in a few centres in Africa to allow the collection of the facts by which the incidence and types of cancer among Africans could be established. There is now emerging an extremely intriguing picture. Certain facts can already be clearly recognized. Firstly, the different age-structure of the population will influence both the incidence and the types of cancer; secondly, inherited features will predispose towards certain types, an example being the pigmented skin rendering melanomata more common; thirdly, local custom may encourage cancer at certain sites—the absence of circumcision and the low standards of personal hygiene are probably related to the high incidence of carcinoma of the penis. In rather a different category are those forms of malignant disease which arise as a complication of skin diseases common in Africa, for example, ulcer-cancer of the leg, which arises only in a tropical ulcer.

Somewhat, but not completely, distinct are those cancers which arise often in chronically diseased organs, but in which the connection is far more tenuous and is not so obvious as in the case of ulcer-cancer. An example is salivary gland carcinoma, which is common in Africa and is possibly related to chronic degenerations and scleroses which arise due to malnutrition, but the relationship is not so clear as it is in the case of hepatic carcinoma complicating cirrhosis—a combination that has been the subject of many speculations. However imperfect may be the direct chain of evidence that leads from fatty liver in infancy to liver carcinoma in adults there is little doubt that the chain exists and that a poor diet in adult life may be a contributory factor. An excellent diet might restore the damaged liver to normal appearance and function but this, like so much else in African medicine, will remain uncertain until it has been proved by controlled observation.

In addition to all the conditions in certain tissues which favour the development of carcinoma, there is the more subtle question of sensitizing agents, amongst them oestrogens and other carcinogens, which must also be the subject of speculation for the time being (Davies, 1949, 1952b).

6. The physique of Africans

In comparison with European adults, African adults are usually judged to be of inferior physique, although there are exceptions such as the Warri of Nigeria (Nicol, 1952) and the Masai of Kenya (Orr and Gilks, 1931). Hailey (1938) remarked that the experience of the allied forces in the East African campaign " furnished unhappy proofs of the wide incidence of physical disabilities . . ." and the physical condition of the men of Equatorial Africa ". . . has proved to be so low that little or no demand is now made on that territory for recruits ". Anderson (1943) reported a very high rate of rejection on medical grounds of volunteers for military service in the 1939-45 war, and said that poor nutrition was the cause of many of the rejections. Many surveys (for example, those of Trowell, 1949 ; Nicol, 1949 ; Colbourne, Edington and Hughes, 1950–51 ; Smith, 1950) have stressed the poor physique of Africans.

It might be thought likely that a few months of good feeding would cause considerable improvement in physique. A team led by Kekwick (1945, personal communication) investigated three groups of East African soldiers, one of men who had been recently recruited and others of men who had received army rations for six to twelve months. The rations, which provided about 100 g. protein and 3000 calories daily, and included meat daily, caused some improvement in the ratio weight to height, but did not always remove signs which were considered to be due to malnutrition such as discoloration and alteration in the texture of the hair and abnormalities of the serum proteins. Infections were thoroughly treated and were not thought to be responsible for the failure to achieve European standards. It may legitimately be argued that the application of such standards was unsound, that the observations were inconclusive because the diet provided only 3000 calories and not the 4000 calories which is more nearly the ration of the British soldier, and that the conditions of service were not ideal for the development of an optimum physique. It may have been significant, however, that in many of the men who died for various reasons, there were signs of liver disease and failure of digestion.

7. Rates of mortality and causes of death

The expectation of life is short in tropical countries. The figures for the East African territories (Table 21) which have been furnished by Dr. C. J. Martin show that a small proportion of the adult population—about 10 per cent—was over 45 years old in 1948. In England and Wales the percentage was 35 (*Registrar-General's Statistical Review*, 1950). In Africa there is an enormous wastage of life in the first years of life, but a large number of young adults also die. Statistics collected in hospitals can always be criticized on the grounds that the hospital population is unrepresentative, but

TABLE 21

Age distribution of African populations in East African territories *

Age groups	Percentage of total in		
	Kenya	Tanganyika	Uganda
Under 1 year	4·5	3·6	2·8
1–5 years	19·0	15·2	14·3
6–15 years	24·6	23·4	23·8
16–45 years	43·2	47·8	47·5
Over 45 years	8·7	10·0	11·6

* This Table has been compiled from data kindly supplied by Dr. C. J. Martin, the Director of the East African Statistical Department. They are based on an enumeration made in 1948.

TABLE 22

Ages at death from records of 2718 *autopsies*, 1946–52, *on subjects over* 10 *years old*
(*From Davies*, 1952*b*)

Age (years)	Male		Female	
	Number	Percentage	Number	Percentage
11–20	197	8·6	60	13·8
21–30	619	27·2	117	26·8
31–40	464	20·4	77	17·7
41–50	246	10·8	33	7·6
51–60	108	4·7	5	1·1
61–70	34	1·5	1	—
70	5	0·2	0	—
" Adult "	598	26·1	140	32·0
" Old "	11	0·5	3	1·0
Totals	2282	100·0	436	100·0

figures for autopsies at Kampala (Davies, 1947, 1948c, see Table 22) support Dr. Martin's figures for the age distribution of the population.

TABLE 23

The most common findings in 2994 autopsies at Mulago, 1931–46
(*From Davies,* 1947)

Lobar pneumonia	462
Tuberculosis	354
Bronchopneumonia	248
Malnutrition	243
Syphilis	232
Nephritis	215
Cirrhosis of liver	181
Enteric fevers	152
Peritonitis	142
Cancer	135
Septicaemias	126
Meningitis	120

Note.—In a total of 144 neoplasms reported by Davies (1947) there were 85 carcinomas (29 primary growths of the liver, and 5 of the stomach), 31 sarcomas, 8 leukaemias, 7 gliomas, 5 teratomas, 4 Hodgkin's disease, and 4 endotheliomas.

In 3705 autopsies, Davies found 229 deaths from cardiac failure. There were 71 cases of hypertensive renal disease, 48 of aortic syphilitic disease and 23 of endocardial fibrosis.

TABLE 24

Findings in 1000 *consecutive autopsies at Nairobi*
(*Vint,* 1936–37)

Pneumonia	298
Tuberculosis	132
Violence	108
Septicaemias	100
Disease of the cardiovascular system	56
Typhoid	51
Malaria	36
Plague	35
Diseases of the urinary system	33
Dysentery	29
Neoplasms *	26
Cerebrospinal meningitis	20
Diseases of the liver	17
Intestinal obstruction	13
" Infantile oedema "	8
Syphilis and broncho-pneumonia	6
Asphyxia	6
Asthenia and terminal pneumonia	4
Food deficiency	4
Diabetes	3
Encephalitis lethargica	3
Status lymphaticus	3
Hodgkin's disease	2
Pernicious anaemia	2
Relapsing fever	2
Shock, surgical	2
Trypanosomiasis	1

* Included 16 carcinomas (of which 8 were primary cancer of the liver, and 3 were of the stomach), 7 sarcomas, 2 epitheliomas and 1 hypernephroma.

If children under 10 years of age were excluded, the average age at death was about 30 years.

The most common conditions found at autopsies at Mulago Hospital, Kampala, in the years 1931–46 and the causes of death in a series of 1000 post-mortem examinations carried out on Africans by Davies (1952b) in Kampala and by Vint (1936–37) in Nairobi are given in Tables 22, 23 and 24. Pneumonia and tuberculosis occupy the first place in both lists ; they occupy high places in similar lists compiled from British statistics. Infections which are specifically tropical appear to be of much less importance.

It is impossible to correlate the cause of death with the states of malnutrition which have been mentioned in this book. It is also impossible to visualize clearly the social consequences of so low an average age at death as the above data suggest. The evidence which has been briefly reviewed points to undernutrition as a factor of immense importance, but it may be that its full significance will not be realized until malnutrition is abolished. It requires little imagination to realize how immense the results of abolition might be.

APPENDIX

A LIST OF VERNACULAR NAMES USED FOR KWASHIORKOR

	Tribe	*Name*
Belgian Congo	Bambala	*Kibuka*
	Feshi	*Kibengi*
	Kasai	*Diboba, Lupussu, Nzadi, Mbuaki*
	Ruanda	*Gatuku, Imbeho, Irungu*
French Equatorial Africa	Bandas Lindas	*Daçaga*
Gold Coast	Akim	*Otrako, Owuo mpumpungya*
	Ashanti	*Akwosi*
	Ewe	*Kyagyavi*
	Fanti	*Abusamba*
	Ga	*Kwashiorkor*
	Hausa (low)	*Jeredi*
	Tara	*Busanga*
Nyasaland	Achawa	*Ndaka Kutapana*
	Ahengo	*Chiulira*
	Angoni	*Chiulira*
	Ankhonde	*Chiulira*
	Anyanja	*Ndaka Kutapana*
Uganda	Acholi	*Neto*
	Dama	*Yewigo*
	Ganda	*Obwosi, Musana*
	Gwere	*Wose*
	Haya	*Mushana*
	Kakwa	*Oletete*
	Kiga	*Mutuku*
	Nkole	*Wamutuku*
	Nyoro	*Kwengera*
	Samia	*Emowa*
	Toro	*Elyosi*
Oceania	—	*Ndambe*
Java	—	*Sakit abu*

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